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# LAURENCE-MOON-BIEDL SYNDROME

## ITS RELATION TO THE GENERAL PROBLEM OF RETINITIS PIGMENTOSA

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In recent years, with the advent of newer knowledge concerning vitamins, hormones and the autonomic nervous system, many clinicians have shown renewed interest in the problem of the pathogenesis of retinitis pigmentosa. As a result patients with this disease have been gorged with vitamins, plied with hormones and subjected to cervical sympathectomy in an effort to arrest or cure the condition. Without wishing to be therapeutic nihilists, we believe that these efforts have been misguided. This belief has been reenforced by a study of the Laurence-Moon-Biedl syndrome in 2 instances.

In view of the fact that classic examples of the Laurence-Moon-Biedl syndrome are so rare as to be of great interest and are full of significant implications with regard to the polyglandular and retinal manifestations, it is felt that these cases are worthy of report.

### REPORT OF CASES

CASE 1.—A. Z., a 12 year old white Cuban boy, was referred on Aug. 9, 1935, to the consultation service at Mount Sinai Hospital. There was no parental consanguinity. One relative on the father's side was said to have had polydactyly. The patient, an only child, was born with six toes on each foot, and the extra toes were removed shortly after birth. His development was apparently normal up to the age of 6 years, when his mother noticed that his vision was poor. At about this time he also began to gain weight rapidly.

*Examination.*—The boy was 4 feet and 11¾ inches (151.8 cm.) tall and weighed 136½ pounds (62 Kg.). He was short and obese, with a typical feminine type of fat distribution about the breasts and hips and a suprapubic fat pad. The face was rather large. Prominent raphes were on the hard palate. The fingers were tapering. There was a scar of the excised sixth toe on each foot. The penis was small. No pubic hair was present. The median raphe and the corrugations of the scrotum were lacking. The testes had descended. The skin was soft and the hair silky.

From the Consultation Service of the Mount Sinai Hospital and the Neurologic Service of the Montefiore Hospital.

Examination of the eyes gave the following data: In both the left and the right eye, vision, corrected, was 15/20, with —0.75 cyl., axis 180°. External examination showed that the pupillary reactions and muscle balance were normal. The visual fields (fig. 1) were markedly contracted in both eyes, in the right more than in the left, but central vision was well preserved. The media were clear, and there were no changes in the lens. The fundus showed a waxy nerve head and thin vessels. There was a sparse but definite deposit of pigment in the periphery of each fundus which was superficially placed and of a "bone-corpuscle" type.

The patient showed no gross behavior disturbance and exhibited a rather placid disposition. His mental age according to the Terman revision of the Binet-Simon test was 9 years, giving an intelligence quotient of 70 and placing him in the high-grade moron group. The psychologist described him as a well mannered boy who showed good cooperation but had slow reactions.

*Laboratory Findings.*—The blood count was normal. Urinalysis showed a faint trace of albumin. The Kahn reaction of the blood was negative. Tests of the blood sedimentation rate and dextrose tolerance gave normal results. The basal metabolic rate was —16 per cent.

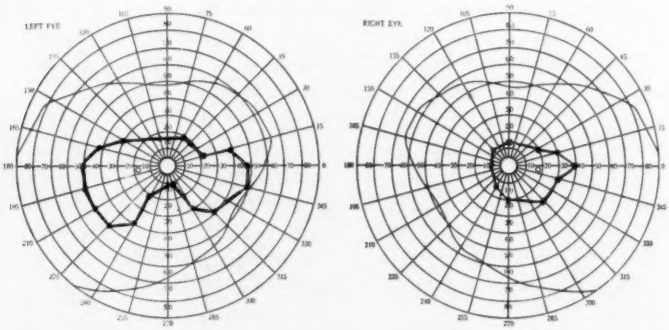


Fig. 1 (case 1).—The visual fields were plotted with 5 mm. test objects. The color fields were contracted to within 10 degrees of the test object.

A roentgenogram of the skull showed that the sella turcica was normal in size and shape. No erosion of the clinoid processes, no evidence of increased intracranial pressure and no unusual shadows in the cranial vault were observed.

Case 2.—J. R., a 14 year old Jewish boy, was admitted to the neurologic service of the Montefiore Hospital on June 5, 1934. The parents were born in Poland and were first cousins. The father was unstable and had a short psychotic episode at one time, from which he apparently recovered. A brother of the father had dementia praecox and was in an institution. The mother, who died at the age of 44, was said to have had a cardiac disorder and to have suffered from frequent convulsive seizures for two years prior to her death. After the birth of this son she had a postpartum psychosis and was maniacal for five months. A brother of the mother also had a cardiac disorder and died at the age of 32. The patient's only sibling, a brother 5 years his senior, was normal in all respects except that he was considered to be somewhat below average mentally.

The patient weighed 6 pounds (2,700 Gm.) at birth, following breech delivery. He began to walk when 1½ years old and to talk at 2 years, in each respect, about

six months later than his sibling. When he was 2 years of age it was noticed that he did not see well and that he groped about for objects as though blind. When he entered school it was noted that he was mentally retarded, and he was placed in an ungraded class. At the age of 9 he began to put on weight rapidly and soon became obese. The father said that the boy drank a great deal of water about this time and also urinated a great deal, but he was unable to state how long this continued. There was no history of any behavior disturbance.

*Examination.*—The boy was 4 feet and 10 inches (147 cm.) tall and weighed 144 pounds (65 Kg.). He was short and markedly obese and appeared three or

Fig. 2 (case 2).—The appearance of the patient at the age of 14. Note the failure of descent of the right testicle and syndactyly of the second and third toes of both feet. (Figures 2 and 3 were reproduced in the volume by L. Lichtwitz entitled "Pathologie der Funktionen und Regulationen," Leiden, A. W. Sijthoff's Uitgeversmaatschappij N. V., 1936.)

four years younger than his stated age (fig. 2). His cheeks were ruddy. He was brachycephalic. The hair was of fine texture. There was no axillary or pubic hair. The mouth was small and the palate high and arched. The teeth slanted inward. Bilateral pes planus and genu valgum were present. The penis was small and undeveloped. The right testis was undescended. The left testis was small and soft. There were striae across the hips. The fingers were short

and tapering. There was polydactylism of the right hand (fig. 3). Syndactylism was present in both feet (second and third toes). Neurologic examination revealed no abnormality except hypotonia. There was a small dimple at the upper end of the gluteal fold which suggested spina bifida occulta, but a roentgenogram of the lower portion of the spine was normal. The blood pressure was 110 systolic and 80 diastolic.

Examination of the eyes showed that vision was markedly reduced; he was able to count fingers at 1 foot (30 cm.) with either eye. Vision could not be improved with lenses. There was moderate divergent strabismus. No muscle palsies were noted, but there was a constant coarse nystagmus in all directions. The pupils were markedly eccentric but equal and reacted normally. There were no posterior lenticular opacities. Both nerve heads were pale and vertically oval. The arteries were extremely thin. Around the periphery of the fundus was a scattered deposit of superficial pigment. Although this did not have the typical "bone corpuscle" appearance, the distribution was characteristic of retinitis pigmentosa. There was some disorganization of the pigment in both maculae (fig. 4).

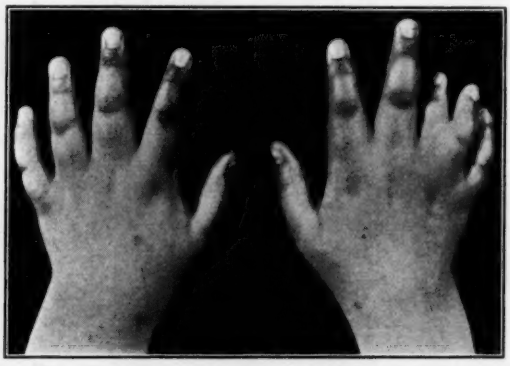

Fig. 3 (case 2).—Showing the polydactylism of the right hand and the short, tapering fingers.

Attempts at studies of the visual fields were unsuccessful because of the poor visual acuity. Central vision seemed absent bilaterally, and the patient was unable to fixate an object. There was no color vision in either eye.

The patient showed no gross behavior disturbance. He appeared to be mentally defective. His mental age according to the Terman revision of the Binet-Simon test was 7 years and 10 months, giving him an intelligence quotient of 54 and placing him in the low grade moron group. However, the psychologist said that the rating was probably too low owing to the fact that the patient was handicapped by poor vision. This was consistent with the clinical impression.

*Laboratory Findings.*—The blood count was normal. Urinalysis was normal. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid gave a negative Wassermann reaction. The cell count, globulin reaction and gum mastic curve were all normal. The blood sedimentation rate, results of gastric analysis and dextrose tolerance were all within normal limits. Chemical study of the blood showed: calcium, 10.8 mg.; phosphorus, 4.6 mg.; cholesterol, 201 mg.;

serum protein, 7.4 Gm. (albumin, 4.2 Gm.; globulin, 3.2 Gm.); sugar, 92 mg., and urea nitrogen, 11.1 mg., per hundred cubic centimeters.

The basal metabolic rates on various occasions ranged between — 17 and — 31 per cent.

Roentgenograms of the skull and sella turcica were normal. The long bones and epiphysial centers were normal for the patient's age. In the region of the fourth finger of the right hand there was an extra digit, consisting of a rudimentary metacarpus and three well formed phalanges.

*Course.*—Anterior pituitary extract parenterally and desiccated thyroid orally were administered without demonstrable change in the patient's condition, either subjectively or objectively. The visual acuity and the appearance of the fundi did

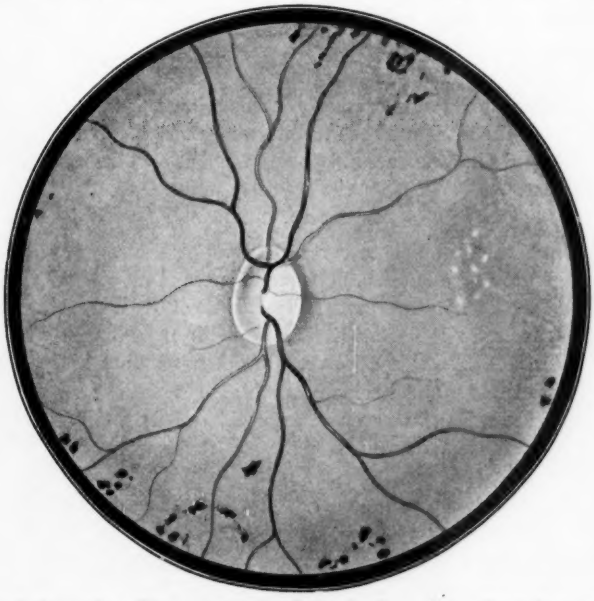

Fig. 4 (case 2).—The appearance of the fundus. Note the pale nerve head, narrow vessels, atrophy in the macula and pigmentary deposits in the periphery.

not change. A few sparse hairs appeared in the pubic region but not in the axillae or over the trunk. In July 1937 the patient was 5 feet and 2½ inches (159 cm.) tall and weighed 175 pounds (79.5 Kg.).

*Summary.*—Both of these patients presented a classic example of the Laurence-Moon-Biedl syndrome. Retinal degeneration, adiposity, genital dystrophy, polydactyly and mental deficiency were observed in each instance. A family history of polydactyly was present in the first case and consanguinity of the parents in the second. The first patient was an only child. The second patient was one of two brothers; the

other boy was said to be normal except for possible mild mental deficiency. The fundus in both cases was fairly characteristic of retinitis pigmentosa, but central vision was well preserved in the first case. In the second, it was markedly impaired, and nystagmus was present. The adiposity and genital dystrophy in both instances were of the so-called hypopituitary type seen in the Fröhlich syndrome. The first patient was born with a sixth toe on the lateral aspect of each foot. The polydactyly of the second patient consisted of an extra digit situated posteriorly in the region of the fourth finger of the right hand; in addition, there was syndactyly of the second and third toes of both feet. Mentally both patients belonged in the moron group, their mental ages being approximately 9 and 8 years, respectively. In neither instance was there any gross behavior disturbance. The laboratory studies in both cases revealed no abnormality except a low metabolic rate. Roentgenograms of the skull and sella turcica were normal. Endocrine therapy was employed in the second case without producing discernible improvement.

## HISTORICAL REVIEW

Although the familial occurrence of atypical retinitis pigmentosa, stunting of growth, adiposity, hypogenitalism and mental deficiency was first described by Laurence and Moon [1] in 1866, it was not until fifty-four years later, in 1920, that it was recognized by Bardet [2] as constituting a distinct clinical syndrome. Bardet noted that his patient also showed polydactyly, and he included this characteristic as part of the syndrome. He failed, however to appreciate mental deficiency and the familial occurrence as essential parts of the syndrome. Biedl,[3] two years later, in reporting 3 cases, recognized the familial occurrence, noted the occasional concomitance of other malformations (atresia ani and deformities of the skull) and pointed out that there were no evidences of cerebral tumor or increased intracranial tension. Solis-Cohen and Weiss,[4] in 1925, reported 4 cases, drew attention to the original description by Laurence and Moon and suggested the name Laurence-Moon-Biedl syndrome, by which the condition has since been generally known. That it might with equal justice have been named the Laurence-Moon-Bardet syndrome has been commented on by several writers.

In the past twelve years a number of papers have appeared on the subject, and almost 100 cases have now been described, including 38

1. Laurence, J. Z., and Moon, R. C.: Ophth. Rev. **2**:32, 1866.

2. Bardet, G.: Sur un syndrome d'obésité congénitale avec polydactylie et rétinite pigmentaire, Thèse de Paris, no. 470, 1920.

3. Biedl, A.: Deutsche med. Wchnschr. **48**:1630, 1922.

4. Solis-Cohen, S., and Weiss, E.: Am. J. M. Sc. **169**:489, 1925.

reports of cases which were discovered by Raab [5] in a search of the literature prior to 1924. In all, however, not more than 50 cases in which the complete syndrome was shown have been described, the remainder being cases in which there was a partial syndrome or in which the diagnosis was doubtful. Reilly and Lisser [6] in their comprehensive survey and summary of the literature found reports of a total of 77 cases, and in only 25 cases was the complete syndrome presented. In 10 others the syndrome was considered as questionably complete. In 26 cases there was only part of the syndrome, and in 16 cases the diagnosis was doubtful. More recently, Cockayne, Krestin and Sorsby [7] have contributed an excellent authoritative study.

## CLINICAL DATA

The complete syndrome as it is known today consists of six cardinal signs—obesity, retinitis pigmentosa, mental deficiency, genital dystrophy, familial occurrence and polydactylism, in the order of frequency. Obesity is present in practically all the cases in which there is no doubt as to the diagnosis; retinitis pigmentosa and mental deficiency, in over 90 per cent; genital dystrophy and familial occurrence, in about 80 per cent, and polydactyly, in about 60 per cent. Other associated signs which are less frequently present are shortness of stature, syndactylism, nystagmus, deafness, atresia ani, genu valgum, pes planus, microcephaly, oxycephaly, congenital heart disease and choreiform movements. The parents are reported as healthy in the majority of cases, but consanguinity was noted in more than a third of the cases in which it was looked for. The syndrome has been described in representatives of almost all races and nationalities. According to Cockayne and his co-workers, there is a genuine preponderance of males over females, in the proportion of 61 to 40.

## DIAGNOSIS

It should be emphasized that it is not necessary to have all six cardinal signs present in order to make a presumptive diagnosis of the Laurence-Moon-Biedl syndrome. The association of retinitis pigmentosa, obesity and genital dystrophy is in itself enough to raise the suspicion that one is dealing with an allied condition or a partial syndrome. Generally speaking, one would hesitate to make the diagnosis in the absence of retinal degeneration. Weiss,[8] however, has described as representing

5. Raab, W.: Wien. Arch. f. inn. Med. **7**:443, 1924.
6. Reilly, W. A., and Lisser, H.: Endocrinology **16**:337, 1932.
7. Cockayne, E. A.; Krestin, D., and Sorsby, A.: Quart. J. Med. **4**:93, 1935.
8. Weiss, E.: Am. J. M. Sc. **183**:268, 1932.

variants of the Laurence-Moon-Biedl syndrome the cases of 2 sisters who showed adiposity, mental deficiency, genital dystrophy and nerve deafness. He said he considered the nerve deafness as an equivalent of or substitute for retinal degeneration and pointed out that these disorders are not infrequently associated. We have encountered in the past year several patients with adiposity, genital dystrophy and a peculiar waxy appearance of the optic disks, and we believe that these cases also are allied to the Laurence-Moon-Biedl group, despite the absence of polydactyly or typical retinal pigmentary degeneration. This group of cases will be described in a separate paper. It need only be mentioned here that it is of importance to distinguish such conditions from other types of adiposogenital dystrophy with which they might be readily confused. The absence of any roentgenologic evidence of an intrasellar or suprasellar pathologic condition and the appearance at an early age of optic pallor, atypical retinal changes, narrowing of the retinal vessels and gross impairment of vision without increased intracranial pressure or other adequate cause are the chief features which set these cases apart from cases of other forms of adiposogenital dystrophy.

## PATHOGENESIS

The pathogenesis of the syndrome has been the subject of considerable discussion. The earlier writers, in describing these cases, held the pituitary gland responsible. Biedl,[8] in 1922, finding the sella turcica normal in his 3 cases, rejected the hypophysial theory and said he considered the disease as due to a diencephalic lesion. In 1924 Raab[5] suggested that a high or massive dorsum sellae was causing pressure on the infundibular stalk, thus disturbing the passage of secretion from the posterior lobe of the hypophysis to the floor of the third ventricle. Raab's views are no longer considered tenable. Ornsteen,[9] in 1932, suggested that the concomitant association of obesity, genital dystrophy, retinitis pigmentosa and mental deficiency is due to a developmental defect of the ectopic zone of the prosencephalon, since the hypothalamus, infundibulum, optic chiasm, retina and end brain all take origin from this zone. He said he considered the skeletal defects (such as polydactylism) the result of accidental coupling of defective somatic genotypic characters. In 1935 Cockayne and his co-workers[7] and Jenkins and Poncher,[10] writing independently, raised the legitimate objection to Ornsteen's theory that the coupling of so rare an anomaly as polydactyly occurred too frequently to be adequately explained on an accidental basis. They suggested, instead, that the syndrome is due to mutation of

9. Ornsteen, A. M.: Am. J. M. Sc. **183**:256, 1932.

10. Jenkins, R. L., and Poncher, H. G.: Pathogenesis of Laurence-Biedl Syndrome, Am. J. Dis. Child. **50**:178 (July) 1935.

two genes in the same chromosome and is inherited as an autosomal recessive characteristic. Priority for this suggestion is given by these authors to Rieger and Trauner.[11]

Cockayne has pointed out that the polydactyly and other skeletal abnormalities are due to a mesoblastic defect, while the rest of the syndrome is dependent on a defect in the prosencephalon, which is epiblastic, and that it is therefore highly unlikely that mutation of a single gene is responsible for the entire syndrome. In cases in which polydactyly does not occur, however, and in cases of a partial syndrome of the type we have mentioned, in which the defect is entirely ectodermal, substitution of a single recessive gene could account for the disease.

Recently Macklin,[12] in a detailed genetic study based chiefly on Cockayne's data, stated the conclusion that the complete syndrome "may be dependent upon two factors, both of which are necessary before the disease becomes evident, one of which is dominant and autosomal, and the other sex-linked recessive."

## PATHOLOGIC PICTURE

Until one year ago no case of the Laurence-Moon-Biedl syndrome had been studied histologically, although Bauer[13] had reported the normal gross appearance of the brain in 1 case. He neglected, however, to make microscopic studies.

In 1936 van Bogaert and Borremans[14] published the first detailed anatomic study of the brain of 1 of these patients. Unfortunately, permission was evidently not obtained for examination of any other organs, since no mention is made of them in the report. The cerebrum, according to the authors, was entirely normal except for small areas of hyaline necrosis in the hypophysial stalk. These were considered of no specific clinical physiopathologic significance, since they are seen in various other unrelated conditions. The pituitary gland and hypothalamus were normal both grossly and microscopically, as was the remainder of the central nervous system. There was hyperostosis frontalis interna in the anterior cranial fossa. "These negative findings," according to the authors, "permit one to exclude with certainty the theory which considers that a malformation or trauma at birth, in the diencephalo-hypophyseal region, is at the basis of the retino-endocrine syndrome of Laurence-Bardet." It is apparent that further postmortem studies of this syndrome will be necessary before anything like a clear picture of the pathologic basis emerges. It is to be hoped, moreover, that such

11. Rieger, H., and Trauner, R.: Ztschr. f. Augenh. **68**:235, 1929.

12. Macklin, M. T.: J. Hered. **27**:97, 1936.

13. Bauer, cited by van Bogaert and Borremans.[14]

14. van Bogaert, L., and Borremans, P.: Ann. de méd. **39**:54, 1936.

studies will include an examination of other glands of internal secretion besides the hypophysis.

### OCULAR FINDINGS

A disturbance in vision, particularly night blindness, is frequently the first symptom to attract attention in these cases. This may occur early in life. Nystagmus may be present, in the form of coarse searching movements, depending on the loss of central vision.

In all the original cases described by Laurence and Moon in an ophthalmologic journal, defective vision and the night blindness characteristic of retinitis pigmentosa were marked. Ophthalmoscopically, scattered areas of pigmentary degeneration were visible in the periphery of the fundi, generally along the course of the retinal vessels. There was no definite atrophy of the optic nerve. In almost all the subsequently described cases some form of retinal degeneration was present. The type of retinal change, however, has varied considerably. Clay [15] has stated that in only 15 per cent of the cases has the typical picture of retinitis pigmentosa been described. By far the greatest number have been recorded as "atypical." In most of the latter cases there have been peripheral pigmentary lesions in varying degrees, with sparing of the macula. In some there has been mild to marked chorioretinal atrophy; in still others, macular lesions similar to those seen in cases of cerebromacular degeneration. Several authors have described cases of retinitis pigmentosa sine pigmento, while Lisser [16] described a case of retinitis punctata albescens (a condition which is allied to retinitis pigmentosa and in which there are pigment deposits, vascular changes and numerous small scattered white spots).

A fairly uniform narrowing of the retinal vessels is practically always present, as is a waxy pallor of the nerve head. Various other ocular findings, such as posterior cortical cataract, strabismus and axial myopia, have also been described in connection with this syndrome.

The pathogenesis of the retinal degeneration in these cases is of great interest, particularly in its application to the broad problem of idiopathic retinitis pigmentosa. The same theories have been proposed to account for both types, although because of the limited number of cases of the Laurence-Moon-Biedl syndrome, the therapeutic attempts in these cases have been fewer. Ornsteen [9] said he was of the opinion that efferent fibers of the optic nerve, controlling chemical changes and movement of pigment in the retina, had been disturbed by a chiasmal defect. Other authors have proposed retinal vascular disease, either primary or secondary to cervical sympathetic dysfunction, vitamin or hormone deficiencies and other possibilities. None of these theories has ever been

15. Clay, G. E.: Tr. Am. Ophth. Soc. **31**:274, 1933.

16. Lisser, H.: Endocrinology **13**:533, 1929.

substantiated in any way. We believe that the evidence obtained from the cases of the Laurence-Moon-Biedl syndrome points to the conclusion that the retinal degeneration, like the other aspects of the syndrome, is an inherited chromosomal factor which is latent from the moment of conception. In this connection it is of interest to note the overwhelming evidence in favor of the hereditary origin of retinitis pigmentosa, presented as early as 1907 by Nettleship [17] in his classic monograph on this subject. He investigated a series of 1,000 families encompassing 1,700 cases. In fully 50 per cent of these cases definite evidence of inheritance or of parental consanguinity was present, and Nettleship stated the opinion that if in the remaining 50 per cent of cases a thorough investigation had been made, the percentage would have been

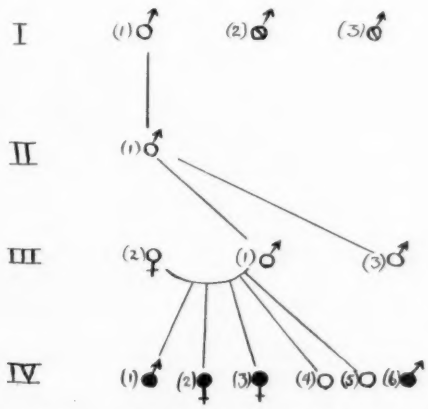


Fig. 5.—The family tree presented by Nettleship,[17] showing transmission of retinitis pigmentosa and other anomalies. IV 4 and 5 each represents a group of 4 siblings, the first having died in infancy and the others being normal. IV 6 is the child of III 3.

even higher. In support of this thesis he presented a number of pedigrees, one of which in particular is of extraordinary interest as regards the problem under discussion and deserves reproduction (fig. 5).

In generation I, 1 was perfectly normal, but 2 and 3 were a deaf-mute and an idiot, respectively. The offspring of $I_1$ in the second and third generations were all normal. However in generation IV, of 11 children, 4 died young, 4 were normal and 3 were idiots with advanced retinitis pigmentosa. In addition, $IV_1$ was partly deaf and had six toes on each foot and six fingers on the left hand, and $IV_3$ had six toes on each foot. Moreover, a paternal first cousin, $IV_6$, was a deaf-mute

17. Nettleship, E.: Roy. London Ophth. Hosp. Rep. **17**:151, 1907-1908.

and blind. In emphasizing the importance of careful genetic studies, which this pedigree exemplifies, Nettleship pointed out, first, that all the diseased offspring were descended from $I_1$, who was normal; second, that the inheritance was discontinuous for two generations, and, finally, that if $I_2$, $I_3$ and $IV_6$ "had not been included in the history (and such omission might easily have occurred) the case could have been claimed as showing the absence of heredity."

Two other facts mentioned by Nettleship in his valuable study have a bearing on the problem under discussion. One is that of 1,381 patients with retinitis pigmentosa whose sex was noted, 845 were males and 536 females, a ratio of 61:39, which corresponds almost exactly with the ratio arrived at by Cockayne [7] in cases of the Laurence-Moon-Biedl syndrome! The other is that fully as many variations occur in the ophthalmoscopic picture of so-called idiopathic retinitis pigmentosa as have been described in the Laurence-Moon-Biedl syndrome. The atypical nature of the retinal degeneration in the latter syndrome, therefore, in no way means that it is unrelated to the idiopathic type. On the contrary, the aforementioned evidence seems to favor strongly the conclusion that the two types of retinal degeneration are closely allied. In this connection it may be noted that Wibaut [18] has differentiated two types of retinitis pigmentosa: a dominant type, which is almost never associated with nerve lesions, and a recessive type, which is associated with deafness and other types of involvement of the central nervous system.

If further evidence were required to indicate the primary degenerative nature of retinitis pigmentosa and to disprove the theory that it is of vascular origin, Verhoeff's excellent histologic study would remove all doubts. Verhoeff [19] has proved conclusively that degeneration of the retinal neuro-epithelium is the primary lesion in retinitis pigmentosa and that such vascular changes as occur are due to secondary thickening of the vascular walls by the increased proliferation of glial tissue.

### LABORATORY STUDIES

Laboratory studies have not revealed any consistent abnormalities. A low basal metabolic rate is the most frequent finding, occurring in over 60 per cent of the cases. Dextrose tolerance is generally normal, with some cases of moderately increased or decreased tolerance. Chemical studies have shown a uniformly normal picture. Recently Klenerman [20] reported 2 cases in which the calcium content of the serum

18. Wibaut, F.: Klin. Monatsbl. f. Augenh. **87**:298, 1931.

19. Verhoeff, F. H.: Microscopic Observations in a Case of Retinitis Pigmentosa, Arch. Ophth. **5**:392 (March) 1931.

20. Klenerman, P. J.: J. Neurol. & Psychopath. **15**:329, 1935.

was high. Both patients, however, were elderly women, aged 72 and 40, respectively, and it is possible that other factors were involved in the disturbed calcium metabolism. Serologic studies have shown a negative Wassermann reaction of the blood in practically all instances.

### ROENTGEN STUDIES

Roentgenographic studies likewise have shown no consistent changes. The sella turcica in most of the cases in which it was examined was essentially normal, with an equal number of cases in which it was larger or smaller than normal. The high or massive dorsum sellae, on which Raab placed so much significance, has been observed in only a few cases. Studies of the long bones have revealed normal nuclear osteogenesis in the majority of instances.

### TREATMENT

The results of treatment in these cases have, on the whole, not been encouraging, although individual authors have published promising reports. In most cases some form of endocrine therapy has been employed, usually a combination of thyroid and pituitary extract. In the case of females ovarian therapy has also been added. The symptom which seems to be most frequently helped is the obesity, which responds somewhat to the use of thyroid. Occasionally, too, after mixed endocrine therapy, these patients seem to show better muscle tone and increased animation, which makes them appear brighter mentally. It is highly doubtful, however, whether any improvement in the basic mental deficiency ever occurs. Of interest is the fact that a number of writers claim to have observed definite improvement in vision after endocrine therapy (Bernhardt,[21] Boenheim,[22] Beck [23] and Reilly and Lisser [6]). In most of these cases, however, the improvement was limited and not correlated with objective improvement in the retinal pathologic condition. Other authors (de Schweinitz,[24] Solis-Cohen [4] and Reilly and Lisser [6]) have claimed to have arrested the failing of vision as a result of therapy, but these conclusions may be questioned, in view of the fact that arrest of failing vision occurs in these cases spontaneously. Surprisingly, there are no reports of any striking improvement in the genital dystrophy, although one would expect that endocrine therapy might be particularly useful in this respect. In view of the numerous favorable reports appearing in recent years concerning the use of the gonadotropic principle of the urine of pregnant women in cases of undescended testicles, it is possible that such therapy, vigorously

21. Bernhardt, H.: Ztschr. f. klin. Med. **107**:488, 1928.

22. Boenheim, F.: Endokrinologie **4**:263, 1929.

23. Beck, H.: Endocrinology **13**:375, 1929.

24. de Schweinitz, G.: Tr. Ophth. Soc. U. Kingdom **43**:90, 1923.

employed, might be of value for the genital dystrophy in the Laurence-Moon-Biedl syndrome.

As regards the polydactylism, of course, surgical treatment is the only recourse.

### COURSE

In all the cases originally described by Laurence and Moon paraplegia eventually developed. This development, however, appears to have been peculiar to this family only and has not been described in any of the subsequent cases. In most of the cases the condition seemed to have been arrested in childhood, and there was little or no subsequent progression in the symptoms. Retinitis pigmentosa rarely progresses to complete blindness. Klenerman's case (that of a woman of 72) shows that the patient may reach an advanced age. Occasionally a reactive behavior disturbance develops.

### SUMMARY

Two classic examples of the Laurence-Moon-Biedl syndrome are described.

A brief survey is given of the present information regarding this condition.

The weight of evidence points to the fact that the pigmentary degeneration of the retina in the Laurence-Moon-Biedl syndrome is a congenital anomaly dependent on an inherited chromosomal factor. We believe that this is a link in the chain of evidence pointing toward the congenital nature of the usual form of retinitis pigmentosa.

Permission to report these cases was granted by Dr. Jorge Muniz, of Habana, and Drs. George Baehr and S. Philip Goodhart, of New York.

# METABOLISM OF VITAMIN C IN RHEUMATOID ARTHRITIS

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On the basis of the occurrence of gross and microscopic changes in the articular tissues of guinea pigs subjected to subacute or chronic scurvy, either alone or in combination with infection, we made the suggestion that vitamin C deficiency may be a significant contributory mechanism in the etiology of some cases of rheumatoid or atrophic arthritis.[1] Brief but suggestive clinical evidence was presented at that time. Subsequently we have endeavored to investigate the problem thoroughly in the clinic. Detailed dietary histories were taken in as many cases as possible. What we consider to be a deficient intake of vitamin C has been a common though not universal finding. A detailed analysis of these records will be made and published later.

The belief that nutritional factors may be important in this disease is not new. Many writers have stressed the importance of nutrition. Hall[2] said: "We are constantly seeing patients with severe arthritis, who for months or years have been eating inadequate or deficient diets.

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This investigation was supported by the Christine Breon Fund for Medical Research and by the California Fruit Growers' Exchange. Hoffmann-LaRoche, Inc., furnished supplies of vitamin C.

1. Rinehart, J. F.; Connor, C. L., and Mettier, S. R.: Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, J. Exper. Med. **59**:97, 1934. Rinehart, James F.: Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis: II. Rheumatoid Arthritis, Ann. Int. Med. **9**:671, 1935.

2. Hall, F. C.: Treatment of Arthritis, Am. Med. **35**:367, 1929.

In such cases, the diet has been the depleting factor." Rowlands [3] and Fletcher and Graham [4] have presented indirect evidence that vitamin B deficiency may operate in the etiology of rheumatoid arthritis. The evidence is based essentially on the frequent observation of atony of the musculature of the colon. Fletcher and Graham gave patients high vitamin diets with particularly generous amounts of vitamin B and observed improvement in the tone of the bowel and frequently much clinical benefit. It is not improbable that vitamin B deficiency states indirectly contribute to the development of arthritis. Nutritional inadequacies are likely to be multiple. Vitamin B deficiency appears to act largely through limitation of the voluntary consumption of food by impairment of appetite. In this way an inadequate intake of vitamin C may follow in its wake, particularly if the selection of food does not include the richer sources of this factor.

A second routine observation in our study has been the determination of the capillary strength by the Dalldorf method.[5] This has been considered an index of "latent scurvy." We realize that there are severe limitations to this method and that many factors other than vitamin C deficiency diminish the capillary resistance. However, it is of significance that we have found the capillary strength almost uniformly and significantly lowered in the atrophic type of arthritis. More recently, particular attention has been directed to the condition of the gums. Swaim's [6] early observation was that in cases of rheumatoid arthritis "the gums are spongy and the teeth decay easily. The mouth resembles that of a scurvy patient." We wish to redirect attention to the prevalence of such gingival changes in this disease. Although it is not invariable, it is remarkably common to find reddened, retracted and edematous gums which are prone to bleed. We do not believe that such a condition can be ascribed to the effect of infection alone. Most students of this disease know how frequently these gingival changes are seen and how often a mouth is encountered from which the teeth have been extracted because of decay or "pyorrhea." It involves no unusual exercise of the imagination to regard the gums as in some respects analogous to the synovial and periarticular tissues. Both are soft tissues applied to dense structures, and both are subjected to repeated trauma. If the synovial membrane is in a boggy, toneless, edematous state and its vessels are unduly fragile and permeable, it (as the gums) may be expected to bleed or

3. Rowlands, M. J.: Rheumatoid Arthritis: Is It a Deficiency Disease? Proc. Roy. Soc. Med. **20**:41, 1927.

4. Fletcher, A. A., and Graham, D.: The Large Bowel and Chronic Arthritis, Am. J. M. Sc. **189**:91, 1930.

5. Dalldorf, G.: A Sensitive Test for Subclinical Scurvy, Am. J. Dis. Child. **46**:794 (Oct.) 1933.

6. Swaim, L. T.: Atrophic Arthritis, Rhode Island M. J. **6**:51, 1923.

ooze plasma and, with the deposition of fibrin, to form a bridge for the growth of granulation tissue and extension of a pannus into the articular cavity. Further, such tissues would be predisposed to bacterial localization. If the strength of the capillaries of the skin is reduced in rheumatoid types of arthritis, it is reasonably safe to assume that other capillaries are fragile and hyperpermeable. While such considerations may be somewhat "imaginative," we do not believe them to be unreasonable.

The recent chemical identification of vitamin C and the formulation of methods for assay of its content in foods, urine, tissues and blood have afforded a more direct and perhaps more scientific method of approach to the problem.

We [7] have previously reported on work confirming the observations of Farmer and Abt [8] that the vitamin C level of the blood plasma is an accurate index of the immediate nutritive state of a person relative to vitamin C and that in "normal" persons it parallels the intake. We have briefly recorded the finding of low vitamin C values in rheumatoid arthritis.[9] The present report represents an extension of this study.

## METHODS

With rare exceptions all specimens of blood analyzed for vitamin C were drawn during the fasting or postabsorptive state. This we consider essential for satisfactory comparative data. The analytic method employed was that originally reported by Farmer and Abt,[8] in which the blood plasma is deproteinized with tungstic acid and the filtrate titrated with 2, 6-dichlorophenolindophenol. Determinations were made promptly, and due caution was exercised for prevention of oxidation. This method we have found to be reliable and accurate.

## CASES STUDIED

The data of this report include observations on 120 medical students as "normal" controls, 26 patients with more or less classic rheumatoid arthritis and 29 patients with less classic arthritis of the rheumatoid type. All the patients exhibited some evidence of activity of the rheumatic process and were seen subsequent to January 1936. In addition, there were 13 patients with gonorrheal arthritis and 12 with hypertrophic arthritis.

## PLASMA VITAMIN C IN CONTROLS

The "normal" group showed values for the vitamin C content of the plasma ranging from 0.22 to 1.45 mg. per hundred cubic centimeters,

7. Greenberg, L. D.; Rinehart, J. F., and Phatak, N. M.: Studies on Reduced Ascorbic Acid Content of the Blood Plasma, Proc. Soc. Exper. Biol. & Med. **35**:135, 1936.

8. Farmer, Chester J., and Abt, Arthur F.: Ascorbic Acid Content of Blood, Proc. Soc. Exper. Biol. & Med. **32**:1625, 1935.

9. Rinehart, J. F.; Greenberg, L. D., and Baker, F.: Reduced Ascorbic Acid Content of Blood Plasma in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **35**:347, 1936.

with an average of 0.7 mg. The individual distribution for this group, contrasted with that for the arthritic patients, is shown in chart 1. It should be pointed out that the value 0.7 mg. is an average and probably falls below what should be considered optimal. Our present opinion remains essentially as previously reported,[7] i. e., that during fasting cevitamic acid levels of the plasma below 0.7 mg. are probably suboptimal. Levels ranging between 0.7 and 0.9 mg. appear to be adequate, and levels below 0.5 mg. must be considered low. Several of the controls showing the lowest vitamin C levels presented findings, such as gingivitis and lowered capillary strength, that might be considered as evidence of vitamin C deficiency.

### PLASMA VITAMIN C IN ARTHRITIS

It will be seen from chart 1 that the patients with active true rheumatoid and rheumatoid types of arthritis exhibited initial vitamin C values

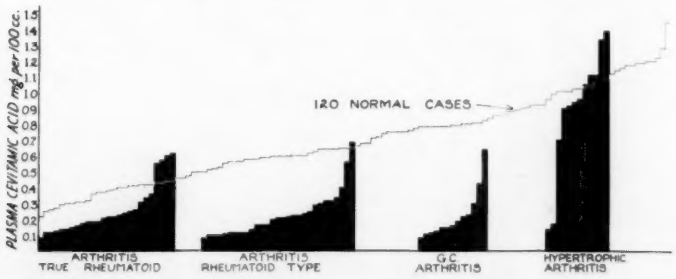


Chart 1.—Distribution curve of the cevitamic acid content of the plasma of normal controls and of patients with arthritis. *G. C.* indicates gonococcic.

of the blood plasma that were uniformly in a strikingly low range. For the 26 patients with more or less classic rheumatoid arthritis, the range was from 0.09 to 0.68 mg. per hundred cubic centimeters, with an average of 0.23 mg. Ninety-three per cent of the values were below 0.5 mg., and 76 per cent were below 0.3 mg. (i. e., at markedly low levels). Essentially similar data apply to the 29 patients with arthritis classified as of "rheumatoid type." Interestingly, the smaller series of patients with gonorrheal arthritis also showed evidence of vitamin C deficiency. The significance of this will be considered presently. The distribution for patients with hypertrophic arthritis was above that for the normal controls.

Chart 2 shows a distribution diagram of the cevitamic acid values for 120 normal controls contrasted with those for the 55 patients with active rheumatoid or rheumatoid types of arthritis. The average value

for the controls was 0.7 mg. per hundred cubic centimeters, and for those with arthritis, 0.24 mg. Eighty-nine per cent of those with arthritis (rheumatoid and rheumatoid types) showed values below 0.5 mg., and 74.5 per cent showed values below 0.3 mg. For the control series only 26.6 per cent of the values were below 0.5 mg., and 4.2 per cent were below 0.3 mg. Without doubt some of the controls had a suboptimal or inadequate intake of vitamin C. It should be pointed out that the great majority of the patients with rheumatoid arthritis, although showing clinical or laboratory evidence of activity, were ambulatory and were seen in the outpatient department. They were not suffering from acute intoxication, and only a few had suffered any recent acute illness. There

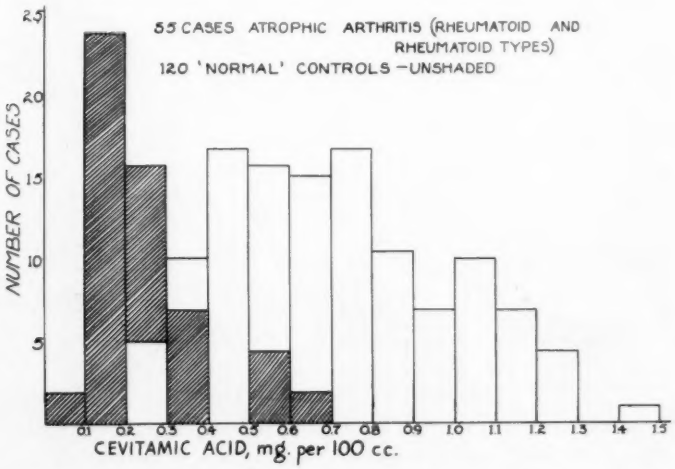
55 CASES ATROPHIC ARTHRITIS (RHEUMATOID AND RHEUMATOID TYPES)
120 'NORMAL' CONTROLS —UNSHADED
NUMBER OF CASES
25
20
15
10
5
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
CEVITAMIC ACID, mg. per 100 cc.

Chart 2.—Distribution diagram of the values for the cevitamic acid content of the plasma.

is no reason to believe that the values recorded for the vitamin C content of the blood did not represent habitual levels.

### RESPONSE OF CONTROLS AND ARTHRITIC PATIENTS TO SUPPLEMENTARY INTAKE OF VITAMIN C

In certain of the controls and of the patients with arthritis it was possible to study the response of the blood plasma levels to extra supplements of vitamin C. Thirteen of the controls who showed initially low values for the cevitamic acid content of the blood were given a daily oral supplement of 100 mg. of vitamin C, and subsequent deter-

minations were made. These cases are represented graphically in chart 3. They not only afford convincing evidence that the vitamin C content of the plasma parallels the intake but for the most part show surprisingly prompt rises to levels within the normal range. The 2 patients who showed the lowest initial plasma levels (P. F. and F. O. D.) and who exhibited delayed rises were probably suffering from subclinical deficiency. Both showed gingival changes, lowered capillary strength and a dietary history rated as low in vitamin C. The average response of this control group is indicated by the dotted line. This line is superimposed as a guide in the comparable graphs for the arthritic patients.

Perhaps more convincing evidence of deficiency than that shown by the initially low vitamin C values in the cases of rheumatoid arthritis

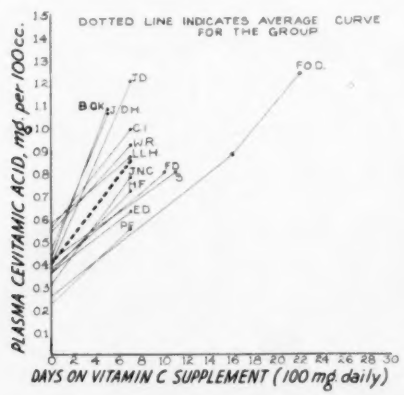


Chart 3.—The response of the blood plasma to the administration of vitamin C. These 13 controls showed initial low levels.

is found in a study of the responses to supplementary feeding of vitamin C. Charts 4 and 5 illustrate changes in blood levels following the administration of extra supplements of vitamin C (either as orange juice or as cevitamic acid). Data for all cases in which enough determinations were available for graphic representation are shown. The daily supplement was 100 mg. or more of cevitamic acid. Supplements other than this are indicated in individual curves. No restriction was placed on the diet; in fact, no other instruction was made regarding the dietary intake. In a number of instances a moderately generous intake of vitamin C was included in the patient's usual diet. It will be seen that a considerable amount of extra vitamin C was required to bring the blood level within a normal range. In the cases of rheu-

matoid arthritis (chart 4) an average of somewhat more than 2 Gm. of extra vitamin C supplement was needed to bring the vitamin C level up to the lower limits of normal (leaving out of consideration the patients who failed to show a significant rise). This value is in the

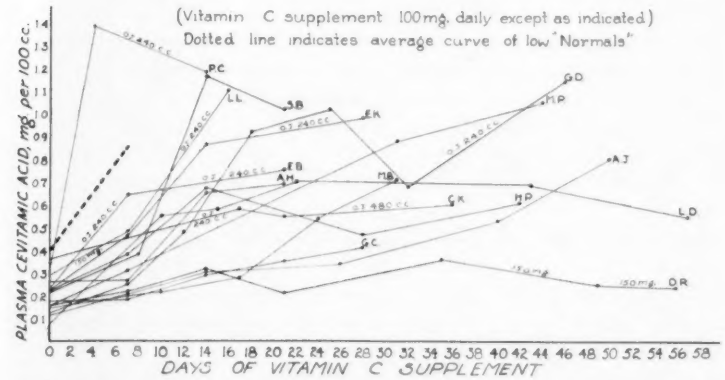


Chart 4.—The response of the blood plasma to the administration of a daily supplement of vitamin C in cases of rheumatoid arthritis. *O. J.* indicates orange juice.

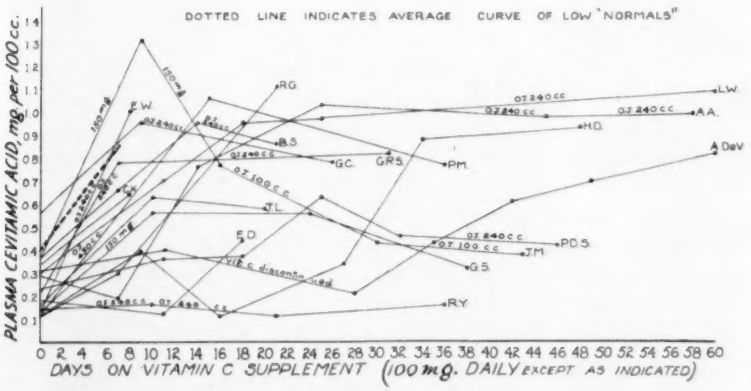


Chart 5.—The response of the blood plasma to the administration of vitamin C in cases of arthritis of the rheumatoid type.

range of that required to saturate a deliberately depleted person.[10] In the cases of rheumatoid arthritis there was, on the average, a delay

10. O'Hara, P., and Hauck, H. M.: Storage of Vitamin C by Normal Adults Following a Period of Low Intake, J. Nutrition **12**:413, 1936.

of one week before any significant elevation of the plasma occurred. In certain cases there was a remarkably delayed response. Similar but somewhat less refractory responses were noted in the cases of arthritis of the rheumatoid type (chart 5). In several instances in both groups there was no significant plasma response after prolonged controlled dietary supplements. The precise metabolic fault in these cases has not been determined. One of the most refractory cases was that of D. R. (chart 4). Although a controlled vitamin C supplement was maintained in this case much longer than the fifty-eight days shown in the graph, no significant rise in the plasma level occurred. That the fault in this instance was probably not one of absorption is indicated by a recent determination of the urinary excretion of vitamin C. In the twenty-four hour period of observation, 44 mg. of vitamin C was excreted, although during fasting the blood level was only 0.11 mg. per hundred cubic centimeters. Such cases require more careful study. A lowered renal threshold is a possible mechanism. This person is one of a number whom we have observed who apparently had a basic fault in vitamin C metabolism. Such persons often give a history of a moderate or generous intake of vitamin C in their diet, but in spite of this they show depressed vitamin C levels and persistent smouldering arthritic activity. It appears then that deficiency of vitamin C may exist in the presence of an adequate intake.

### GONORRHEAL ARTHRITIS

Gonorrhea could be reasonably established in the etiologic background of only 13 persons. It is possible that in some of the cases of arthritis of the "rheumatoid type," gonorrhea had been contributory. Initial vitamin C values for the patients with gonorrheal arthritis were, in general, low, ranging from 0.09 to 0.64 mg. per hundred cubic centimeters and averaging 0.22 mg. The majority of the patients were not febrile or severely ill at the time of examination. It is interesting to speculate on the significance of this finding. That infection may serve to deplete the organic reserve of vitamin C is well supported by considerable evidence.[11] Another interpretation that naturally suggests itself is that arthritis develops because of a lowered resistance of the articular tissues to bacterial localization secondary to mild or moderate vitamin C deficiency. That the deficiency is in most instances somewhat milder in these cases is indicated by the relatively prompt rise of the vitamin C level with a supplemented intake (chart 6). That

11. (*a*) Faulkner, J. M., and Taylor, F. H. L.: Vitamin C and Infection, J. Clin. Investigation **15**:472, 1936. (*b*) Perla, David, and Marmorston, Jessie: Rôle of Vitamin C in Resistance, Arch. Path. **23**:543 (April) 1937.

one of the patients (C. L.) whose data are given in chart 6 was suffering from scurvy seems beyond reasonable doubt. The dietary history indicated a low intake of vitamin C, and the capillary strength was reduced. The gums were reddened and edematous and bled easily.

## THERAPEUTIC RESULTS

Our data for judgment of the therapeutic value of a high intake of vitamin C in arthritis we do not believe are adequate for statistical analysis, but clearcut clinical improvement has occurred in the majority of cases. The only other form of treatment in our cases has been selective physical therapy. It is interesting that in the majority of instances of recurrence we have found the cevitamic acid content of the plasma

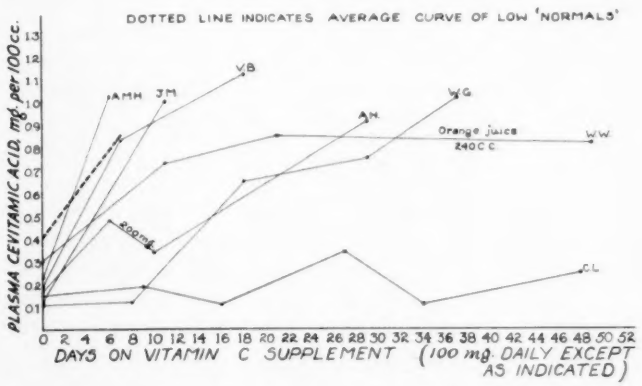


Chart 6.—The response of the blood plasma to the administration of vitamin C in cases of gonorrheal arthritis.

depressed. The most satisfactory clinical responses occurred in the cases in which there was a satisfactory rise of the cevitamic acid content. The results in the few cases in which daily intravenous administration of the sodium salt of cevitamic acid was combined with supplements of vitamin C by mouth have been particularly encouraging.

## COMMENT

As has been pointed out, it is obvious that the vitamin C content of the plasma is an index only of the immediate nutritive status of the individual relative to this food factor. However, the practically uniform finding of low vitamin C values in a large series of cases of rheumatoid arthritis must be significant. Sherwood[12] has briefly

12. Sherwood, K. K.: Clinical Significance of Vitamin C, Kings Co. Hosp. Bull. **4**:7, 1937.

recorded similar observations, and Perla [11b] has cited unpublished data of Finkle that appear corroborative. Except in a few instances, we do not believe that our patients were suffering from degrees of infection that would cause vitamin C depletion. In fact, the majority were afebrile, and in many no infection could be demonstrated. We do not deny the influence of infection, which has been emphasized particularly by Cecil.[18] However, we do not believe that infection alone is responsible for the disease. In some cases a chronic lack of vitamin C may prepare the articular tissues for localization of bacteria of low virulence. Convincing evidence of deficiency is indicated in the curves showing delayed saturation following the giving of a supplement. The data here recorded are considered as conclusive as such data can be and to afford strong support for the thesis that chronic vitamin C deficiency is of major etiologic significance in many cases of rheumatoid arthritis or polyarthritis of the rheumatoid type. If subacute or chronic vitamin C deficiency produces comparable arthritis in experimental animals, it is not unreasonable to believe that it may do so in man.

## SUMMARY AND CONCLUSIONS

The cevitamic acid level of the blood plasma during fasting is almost uniformly and severely lowered in rheumatoid and rheumatoid types of arthritis. In the majority of cases the blood level rises after the administration of vitamin C. Usually this rise is delayed. These data indicate the existence of vitamin C deficiency in arthritis of this type, and we believe they afford significant support for the thesis that chronic deficiency of vitamin C is an important factor in the etiology of the disease. Some patients appear to present a fundamental fault in vitamin C metabolism. The plasma levels during fasting fail to rise after prolonged administration of generous supplements of vitamin C, although the urinary excretion may be relatively high. A lowered renal threshold is a possible mechanism. Low vitamin C levels are the rule in gonorrheal arthritis. It is suggested that deficiency of vitamin C predisposes to bacterial localization in this group and possibly also in the other groups. In the small series of cases of hypertrophic arthritis the plasma values were almost uniformly high. Apparently deficiency of vitamin C may exist in the presence of an ordinarily adequate dietary intake. Our preliminary therapeutic observations have been distinctly encouraging. Such studies to be conclusive should be rigidly controlled and should be extended over an adequate period.

13. Cecil, R. L.: Rheumatoid Arthritis, J. A. M. A. **100**:1220 (April 22) 1933.

## DISCUSSION

DR. M. P. SCHULTZ, Washington, D. C.: Since Dr. Rinehart and his colleagues made the brilliant observation that in guinea pigs subject to the combined influence of chronic scurvy and infection with group C hemolytic streptococci a characteristic form of nonpurulent carditis develops, these experiments have been repeated, as has just been stated, by four groups of investigators. The findings of Dr. Rinehart have been confirmed, in that cardiac damage of the type he originally described develops in guinea pigs subjected to chronic scurvy plus infection or, as appears to be indicated by recent work, uncomplicated acute scurvy. It should be pointed out, however, that none of the subsequent observers considers that these lesions bear a close resemblance to those of rheumatic fever.

From the clinical standpoint, as Dr. Rinehart has mentioned, the subject has received the attention of several investigators. Warner, Winterton and Clark in a dietary study found that rheumatic children consume as much or more food containing vitamin C than do controls. They stated, indeed, that on the basis of their study the relation between rheumatic fever and scurvy suggested by Dr. Rinehart cannot be supported. The experiments of Perry and his co-workers, in which the degree of vitamin C saturation of patients with rheumatic fever and of controls was studied, also did not support this hypothesis.

Dr. Rinehart has described in part the experiments of this type which were undertaken at the Hospital of the Rockefeller Institute—work with which I was associated. Because evidence of C hypovitaminosis was by no means found to be regularly associated with rheumatic fever, because similar degrees of deficiency were found to be present in other disease states and because treatment with large doses of the vitamin were ineffective, we concluded that scurvy is not an important factor in the pathogenesis of rheumatic fever. We considered that those experiments in which subjects received 100 mg. of cevitamic acid daily in addition to their habitual diet (which in many instances did not seem to be inadequate) for several months before rheumatic fever developed in severe and typical form were of especial significance. These patients received several times the quantity of the vitamin considered sufficient to prevent the development of scurvy, and when their degree of saturation with cevitamic acid was tested after the development of rheumatic fever, no severe degree of C hypovitaminosis was found to be present.

The work of Abassy, Hill and Harris has been described at some length by Dr. Rinehart as in support of his conclusions. These observers found an apparent degree of scurvy in most but not all patients with acute or chronic rheumatic fever. The findings in this group differed little from those for patients with active or semiactive tuberculosis. In patients with quiescent tuberculosis, on the other hand, and in controls a comparable degree of hypovitaminosis was not present. These authors pointed out, indeed, that in cases of active infection, either rheumatic or tuberculous, there is frequently a deficit with respect to this vitamin, whereas in the absence of active infection this is not so likely to occur. They stressed the point that in the group of patients with quiescent tuberculosis, active infection is no longer present—the process has healed. They were emphatic that on the basis of their work it cannot be concluded that in patients with rheumatic fever there is any alteration in vitamin C metabolism which is not present also in patients with other infections.

Investigators in this field are unanimous in the conclusion, so strikingly demonstrated by the extensive work of Dr. Rinehart, that degrees of C hypovitaminosis do occur in patients with rheumatic fever. It would indeed be surprising if this were not the case. In the past few years about a dozen studies have been made of

vitamin C metabolism in various infections. The degree of saturation with this vitamin has been investigated by measuring the excretion after test doses or by estimating the cevitamic acid content of the blood of patients with various infections, for instance, tuberculosis, pneumonia, typhoid fever, furunculosis and sepsis. Studies of this character have demonstrated a tendency to C hypovitaminosis in all the infectious states which have been investigated. Two of these papers are especially pertinent; Widenbauer determined the daily dose of vitamin C necessary to maintain excretion at an optimum level and compared variations in the quantity requisite with alterations in the erythrocyte sedimentation rate. There was a striking parallel; with increased severity of the infection, as indicated by an accelerated sedimentation rate, there was an increase in the amount of vitamin necessary to maintain the balance. This author, familiar with the work of Dr. Rinehart, included cases of rheumatic fever in the series. The behavior of these patients differed in no way from that of patients with other types of infection, chiefly tuberculosis. Graphs were presented demonstrating that a patient in balance with respect to vitamin C with a certain daily dose requires a greatly increased quantity immediately on the development of a dental abscess, but his requirement returns to the former level when the abscess is drained. A few days later a corresponding rise and fall of the sedimentation rate takes place. This parallel between the amount of cevitamic acid required and the sedimentation rate was regularly demonstrable.

The other investigation which seems particularly pertinent to the present discussion was carried out by Baer, who observed the degree of vitamin C subnutrition by means of saturation tests of 35 patients with acute pharyngitis. Hypovitaminosis with respect to vitamin C was so regularly found and was of such extreme degree that this author suggested that acute pharyngitis may be one manifestation of this deficiency condition. The 35 patients studied represented a wide range of ages, and although the local infection of the throat was in many cases severe and the degree of scurvy in each instance was definite, neither rheumatoid arthritis nor rheumatic fever developed as a complication.

Concerning the careful and extensive study which Dr. Rinehart has described, only two questions occur: The first is regarding the method of titration used. The determination of reduced cevitamic acid by the method of Farmer and Abt possesses certain advantages, in that it is easily and rapidly performed and requires a minimum of chemical manipulation. The disadvantage lies in the fact that reduced cevitamic acid is readily converted to the reversibly oxidized form—a slight degree of hemolysis in the serum, for instance, accelerates this change and may be responsible for false low readings. As reported in the *Proceedings of the Society for Experimental Biology and Medicine,* Dr. Piojan, of Rochester, N. Y., attempting to use the method as originally described by Farmer and Abt (presumably the unmodified method which Dr. Rinehart employed) found it entirely unreliable. Further investigation demonstrated that false low readings were obtained unless the specimens were titrated immediately after the blood was drawn. Dr. Piojan emphasized the fact that no more than thirty minutes should elapse between the drawing of blood and the titration if reliable data are to be obtained. Since Farmer and Abt did not mention the necessity of observing this precaution and in view of the extremely low values which Dr. Rinehart reports, the observations of Dr. Piojan appear to be pertinent. I wish to inquire, therefore, if in the experiments just reported all titrations were performed within the recommended time limit.

The other question is with regard to medication received by the patients. Daniels and his colleagues have reported from Iowa that the administration of

acetylsalicylic acid to febrile children results in increased excretion of vitamin C. These authors suggested that the unusually low figures which Dr. Rinehart reported for children may be the result of depletion of vitamin C reserves by antecedent medication with acetylsalicylic acid. I am aware that Youmans and his colleagues have since reported that in afebrile adults this effect of acetylsalicylic acid could not be demonstrated. Since patients with rheumatic fever are usually febrile children, however, conclusions concerning vitamin C metabolism must be regarded with reservation if the subjects studied had received acetylsalicylic acid or other salicylates. In view of the difficulty in finding arthritic patients, especially those with rheumatic fever, who have not been treated with these drugs, I wish to inquire if Dr. Rinehart eliminated this complicating factor in the present study.

Dr. Rinehart and his colleagues have made a valuable extensive study of vitamin C metabolism in infection. In the light of all information at present available on this subject, however, it would be unjustifiable to conclude that the disturbances in rheumatic fever are of greater significance than those of similar character observed in other infections.

Dr. A. Almon Fletcher, Toronto, Canada: It is not easy to assess the significance of Dr. Rinehart's observations. It is reasonable to propose that behind the development of rheumatic disease there is some chronic nutritional disorder. It is not likely that the answer to this important question will be found in the administration of a few tumblerfuls of orange juice or by the analysis of the patient's diet, because chronic nutritional disorders are likely to be, to a large extent, irreversible or slowly modified by dietetic treatment.

The production in experimental animals by means of vitamin C deficiency of lesions comparable to those of rheumatic fever and rheumatoid arthritis is suggestive but does not by any means prove that these lesions are identical with those occurring in man. It is difficult to believe that many patients with rheumatoid arthritis are suffering from subclinical scurvy. Occasionally the spongy, bleeding gums referred to by Dr. Rinehart are seen, and they undergo prompt improvement with the administration of vitamin C. Much more frequently such changes are absent, and at times patients with rheumatoid arthritis are made worse by the administration of large amounts of fruit.

There is much clinical experience to suggest that patients with rheumatoid arthritis are helped by high vitamin diets, and at times the liberal administration of vitamin C appears to be of value. Such measures suggest that if chronic disturbed nutrition contributes to the development of this disease, the disturbance is of a nonspecific character in which vitamin C may at times be one factor.

Dr. James M. Faulkner, Boston: I find myself in such close agreement with Dr. Schultz' remarks that I have little to add. The question seems to be essentially whether the low cevitamic acid values for the blood which Dr. Rinehart finds in patients with rheumatic fever are a cause or an effect. Now, it has been recognized ever since the publication of the earliest observations on scurvy, three hundred and fifty years ago, that infection is an important predisposing cause of scurvy. Dr. Rinehart has just demonstrated that the blood level of cevitamic acid is usually reduced not only in rheumatic fever but in other infectious diseases the etiology of which is well established. My colleagues and I have had the opportunity at the Boston City Hospital of estimating the blood values for cevitamic acid for patients with and without infection. All these patients had been receiving diets generally considered adequate as to the vitamin C content. For 43 subjects without infection the average cevitamic acid value was 1.31 mg. per hundred cubic centimeters, while for 66 patients suffering from miscellaneous

infectious diseases the average value was 0.64 mg. Among the patients with infection there were 10 with acute rheumatic fever for whom the average value was 0.48 mg. We did not regard the slight difference in average value for the patients with rheumatism and those with miscellaneous infections as significant. We also had the opportunity to study the vitamin C balance of a patient with active pulmonary tuberculosis. The patient was maintained on a diet almost completely lacking in vitamin C and was given measured amounts of pure cevitamic acid. It was found that it took 300 mg. of cevitamic acid daily by mouth to bring the blood level and urinary excretion of this substance to normal. Similar observations in a case of acute rheumatic fever revealed the same increased requirement, namely 300 mg. per day.

It seems to me that Dr. Rinehart's observations might be explained on the basis of a nonspecific effect of infection on the metabolism of vitamin C analogous to the effect of infection on the metabolism of iron or of vitamin B. If vitamin C undernutrition were an important etiologic factor in rheumatic fever one would expect to see rheumatic fever occasionally in the presence of clinical scurvy. I have not yet seen this combination.

Dr. Russell L. Cecil, New York: Dr. Rinehart was kind enough to send me some of his sections last winter, and I was greatly interested in some of the lesions produced in the guinea pig. It seemed to me that while there were some lesions that showed an infiltrative reaction, the infiltration was not as active as is seen in typical rheumatic fever. I should think that controls with other vitamins would be important in this connection. The fact that the patient fails to improve when fed on vitamins is disappointing. The question after all is this: Is this deficiency in vitamin C the cause or the effect of the disease?

Dr. James F. Rinehart, San Francisco: Dr. Schultz has raised a number of questions that are difficult to answer. The data presented here are not considered a final answer to the problem, but I believe they indicate an imperative need for adequately controlled prophylactic and therapeutic studies. The bulk of the evidence available at present indicates that the reduced form of cevitamic acid is the significant and physiologic active form of the vitamin. Dr. Schultz has cited the excellent work of Warren, Winterton and Clark. This study is particularly painstaking, but I do not believe that it is conclusive. A gross estimate of the intake of fruits and vegetables does not give an accurate idea of the vitamin C intake, because of the varied content of this factor in different foods. With respect to the reliability of the methods used, I may say that my colleagues and I have investigated particularly carefully all possible pitfalls in the methods, and the evidence, which we cannot go into at this time, we believe indicates that they are entirely reliable. Data pertaining to the possible influence of acetylsalicylic acid on the excretion of vitamin C are controversial. As far as we know, there is no effect of this drug on the blood level; also many of our patients were not receiving any form of salicylates. We have been aware of Dr. Piojan's criticism of the method and can say without hesitation that it is not valid.

I wish to thank Dr. Fletcher for his conservative discussion of this paper and to reemphasize what has been said. Indeed, the answer to the problem will not be found by giving a few glasses of orange juice to the patients.

Dr. Faulkner has raised a pertinent question, that is, whether the low levels of vitamin C in the blood plasma are not secondary to the disease. This question perhaps particularly applies to acute rheumatic fever. There is every indication that infection itself serves, at least in some degree, to deplete the vitamin C reserve. We believe it to be particularly significant that approximately 75 per cent of the patients with

chronic or inactive rheumatic fever have a significantly low vitamin C level of the plasma. This is in agreement with the work of Abbasy, Harris and Hill. An inactive disease would hardly deplete the vitamin C reserve. There is no reason to believe that the levels recorded do not represent habitual values for these subjects. In patients with rheumatoid arthritis, particularly, only occasionally have we seen severe infection preceding the onset of the disease, and in the patients in whom we have been able to demonstrate focal infection the latter has not been of a degree that might deplete the vitamin C reserve. Most of the patients included in this study were in the outpatient department and were ambulatory and except for the arthritic disability showed no striking manifestations of infection. Obviously, and in our experience, not only are low vitamin C levels of the blood found for patients with rheumatic fever and rheumatoid arthritis, but they have been practically consistently found for patients with these diseases. This consistency makes the finding significant. The question has been raised again why we do not see rheumatic fever in patients with scurvy. I do not believe that any one has sufficient data to answer this question. Obvious scurvy is a late and severe form of vitamin C deficiency. Clinically manifest scurvy is seen practically only in infants and adults. It is uncommon to find recognizable scurvy in a person of the rheumatic fever age group. Is it not possible that this unrecognized scurvy is present in rheumatic fever or rheumatoid arthritis? If a disease resembling rheumatic fever or rheumatoid arthritis can be produced in animals by vitamin C deficiency, it is entirely reasonable that the same deficiency would produce comparable states in human beings. The evidence of this and other studies indicates that significant degrees of vitamin C deficiency exist rather commonly, particularly among poorer persons. Where then are the diseases that result from this? Dr. Cecil has asked why patients fail to improve with an increased intake of vitamin C. An adequate study of the effect of a high intake of vitamin C in these diseases has not yet been made. In some cases the requirement is abnormally high. As Dr. Fletcher has said, the administration of a few glasses of orange juice will not answer the problem. A high intake of vitamin C, controlled by chemical studies of the blood, must be maintained over a long period, and patients must be followed with care for adequate evaluation. Certain of the deformities produced will not be corrected by any method.

In summary, I may say that not only experimental but clinical, epidemiologic and biochemical studies all point to the possible importance of vitamin C deficiency in the etiology of rheumatic fever and rheumatoid arthritis. These data indicate clearly the importance of comprehensive preventive and therapeutic studies. Adequate control and long periods of observation are necessary.

# METABOLISM OF VITAMIN C IN RHEUMATIC FEVER

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Since the suggestion was originally made that vitamin C deficiency may be an important factor in the etiology of rheumatic fever,[1] there has been considerable study of this problem. The concept was based on experimental observations that a pathologic state with certain similarities to rheumatic fever may be produced by subjecting guinea pigs to the simultaneous influence of vitamin C deficiency and streptococcic infection. The reports recorded the occurrence of lesions comparable to those of rheumatic fever in the cardiac valves, cardiac muscle and joints of the experimental animals so treated. The well known epidemiologic peculiarities of rheumatic fever, notably the geographic, seasonal and social incidence, are in accord with such a concept. A conditioning environmental influence is suggested particularly by the dominant occurrence of the disease in the poor.

Stimson, Hedley and Rose [2] soon offered confirmation of the experimental work and added a brief report on the production of a degenerative and proliferative myocardial lesion bearing some resemblance

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1. Rinehart, J. F., and Mettier, S. R.: The Heart Valves and Muscle in Experimental Scurvy with Superimposed Infection, with Notes on the Similarity of the Lesions to Those of Rheumatic Fever, Am. J. Path. **10**:61, 1934. Rinehart, J. F.; Connor, C. L., and Mettier, S. R.: Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, J. Exper. Med. **59**:97, 1934.

2. Stimson, A. M.; Hedley, O. F., and Rose, E.: Notes on Experimental Rheumatic Fever, Pub. Health Rep. **49**:361, 1934.

to the Aschoff reaction induced by intracardial injection of streptococcus toxin in scorbutic guinea pigs. They suggested that the ability of an organism to produce such lesions might, in part, be dependent on its production of toxin. Schultz [3] likewise produced nonpurulent carditis by means of the synergistic influence of chronic scurvy and hemolytic streptococcic infection. He said he considered that the changes only slightly resembled those seen in rheumatic fever. More recently McBroom, Sunderland, Mote and Jones,[4] as well as Taylor,[5] have recorded the occurrence of degenerative and proliferative reactions in the cardiac valves of scorbutic animals in which a factor of infection was not experimentally introduced. They observed no clear difference in their animals in which experimental infection was superimposed on the scorbutic state. It is of significance that for the most part the streptococci used by these authors were derived from human sources and were not satisfactory infecting agents for guinea pigs.[6] In our original work, streptococci derived from guinea pigs and natural pathogens for guinea pigs were used. In our own experience the virulence of the infecting organism is important in the production of the "rheumatic-like" pathologic picture. Furthermore, we believe that some of the lesions produced by us are more like those of rheumatic fever than those described by the authors cited. Taylor recorded the finding of small numbers of bacteria in the cardiac muscle of scorbutic animals not experimentally infected.

All agree that infection alone, in the presence of an adequate diet, does not produce rheumatic-like lesions. Recently several clinical approaches to the problem have been made. Warner, Winterton and

3. Schultz, Mark P.: Cardiovascular and Arthritic Lesions in Guinea-Pigs with Chronic Scurvy and Hemolytic Streptococcic Infections, Arch. Path. **21**:472 (April) 1936.

4. McBroom, Josephine; Sunderland, Douglas A.; Mote, John R., and Jones, T. Duckett: Effect of Acute Scurvy on the Guinea-Pig Heart, Arch. Path. **23**:20 (Jan.) 1937.

5. Taylor, S.: Scurvy and Carditis, Lancet **1**:973, 1937.

6. The observations made on the animals in group 5 of Taylor's series are of particular interest. The four pigs used in that experiment received a basal diet free from vitamin C for four weeks. Hemolytic streptococci (human source) were injected intracutaneously, and thenceforth the pigs received 4 cc. of orange juice per day. All recovered from the scurvy and gained weight continuously for the remaining fifteen weeks of the experiment. They were then killed. "None showed signs of scurvy post mortem. The livers were very fatty and hearts were all slightly enlarged." The mitral valves were all nodular. Histologically the hearts showed perivascular infiltration, edema and proliferative mitral valvulitis. There was massive endothelial cell infiltration of the auricle in one animal. These observations are potentially of considerable significance, and the study should be repeated with a larger series of animals.

Clark,[7] in a detailed dietary survey, found the gross consumption of fresh fruits and vegetables by rheumatic persons to be equal to or greater than that by controls. However, at Christ's Hospital an increase in consumption of fruits and vegetables was associated with a fall in the incidence of rheumatic fever. Other dietary changes, however, were made in the same period, notably an increase in consumption of fat (including butter) and of protein. Although this study was remarkably detailed and exhaustive, it is naturally inconclusive. No accurate index of the consumption of vitamin C is possible from a gross estimate of the intake of fresh fruits and vegetables because of extreme variations in the vitamin C content of foods of this sort. Furthermore, inherent or acquired metabolic faults and depleting mechanisms were not considered.

Faulkner[8] has studied the reticulocyte response in certain chronic infections following administration of generous supplements of vitamin C. A rise of 2 to 4 per cent in the reticulocyte count (young red blood cells) occurred after liberal administration of vitamin C in most cases. This study concerned twenty-seven patients with rheumatic fever, eight with tuberculosis of the bone and two with Still's disease. To us this suggests a reaction following correction of a deficiency.

Perry[9] examined the vitamin C reserve of five patients with active rheumatic fever and six with quiescent rheumatic fever. His study was based on the urinary excretion following test doses of vitamin C. Although these examinations revealed evidence of deficiency in a number of cases, he concluded that "vitamin C-deficiency is not an important factor in the cause of acute rheumatism," although "mild degrees of this deficiency are not uncommon in rheumatic children." Sendroy and Schultz[10] undertook a careful study of the utilization of vitamin C in rheumatic fever. Eight of thirteen patients showed a utilization of the vitamin above the calculated normal. This the authors ascribed to faulty absorption or digestive disturbance. The existence or nonexistence of a deficiency before dietary modification was not studied by them. More recently Abbasy, Hill and Harris,[11] in a direct, uncomplicated experiment, have investigated the problem, studying large numbers of patients. Their series included one hundred and seven patients with

7. Warner, Edwin C.; Winterton, Frank G., and Clark, M. L.: A Dietetic Study of Cases of Juvenile Rheumatic Disease, Quart. J. Med. **28**:227, 1935.

8. Faulkner, James: The Effect of Administration of Vitamin C on the Reticulocytes in Certain Infectious Diseases, New England J. Med. **213**:19, 1935.

9. Perry, C. B.: Rheumatic Heart Disease and Vitamin C, Lancet **2**:426, 1935.

10. Sendroy, Julius, and Schultz, Mark P.: Studies of Ascorbic Acid and Rheumatic Fever, J. Clin. Investigation **15**:369, 1936.

11. Abbasy, M. A.; Hill, N. Gray, and Harris, Leslie J.: Vitamin C and Juvenile Rheumatism, Lancet **2**:1413, 1936.

active rheumatic fever, eighty-six convalescent patients, together with sixty-four controls, and forty-two patients with surgical tuberculosis in the earlier stages of the disease, as well as forty-six with quiescent surgical tuberculosis. All the children were hospital patients and had for some time received in their diet more vitamin C than the reputed minimum standard. These authors found a striking decrease in the excretion of vitamin C (evidence of vitamin C deficiency) of the patients with active rheumatic fever, patients convalescing from rheumatic fever and patients with active tuberculosis. Those with quiescent tuberculosis showed a normal excretion. Further, it was found extremely difficult to "saturate" the rheumatic children with vitamin C. In other words, it was found that the rheumatic children were in a lowered state of nutrition relative to vitamin C, and it was concluded that there is a greatly increased metabolic use of (and need for) vitamin C in rheumatic fever. Accordingly the authors recommended the giving of large amounts of the vitamin both therapeutically and prophylactically. The finding of unsaturation in patients with inactive rheumatic fever and those convalescing from rheumatic fever suggests either an unusual depletion or a greater than average requirement for vitamin C in "rheumatic" children.

Farmer and Abt [12] have recently described a method for the determination of the reduced cevitamic acid content of the blood plasma and have reported that the values obtained by this method parallel the intake of vitamin C and are an accurate index of the nutritive state relative to this food. We [13] have confirmed this work, showing that in normal persons the vitamin C content of the plasma during fasting is an accurate index of the intake of vitamin C and that the data so obtained are comparable to those obtained by studies of urinary excretion. The method affords a simple and direct way of determining the immediate nutritive status of a person relative to vitamin C. If serial determinations are made with a controlled intake of the vitamin, an estimate of the degree of unsaturation can be ascertained. Using this method of study, we [14] reported briefly the almost consistent finding of a low vitamin C content of the plasma in cases of rheumatic fever in which significant modification of the dietary habit had not been made preceding the determination. The present report deals with a more extended study of the problem, similar methods being used. From accumulated evidence

12. Farmer, Chester J., and Abt, Arthur F.: Ascorbic Acid Content of Blood, Proc. Soc. Exper. Biol. & Med. **32**:1625, 1935.

13. Greenberg, L. D.; Rinehart, J. F., and Phatak, N. M.: Studies on Reduced Ascorbic Acid Content of the Blood Plasma, Proc. Soc. Exper. Biol. & Med. **35**: 135, 1936.

14. Rinehart, J. F.; Greenberg, L. D., and Christie, A. U.: Reduced Ascorbic Acid Content of Blood Plasma in Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **35**:350, 1936.

we believe that optimal levels of the vitamin C content of the blood for children are above or at 0.9 mg. per hundred cubic centimeters. Values between 0.7 and 0.9 mg. are probably adequate, but values below 0.5 mg. must be considered low.

The present report is based on a study of forty-two patients with active rheumatic fever and twenty-two with "interval" rheumatic fever without clinical evidence of activity. The great majority of the patients were children. One control group consisted of nineteen children admitted to the University of California Hospital for tonsillectomy. These

TABLE 1.—*Vitamin C Content of the Blood*

| | Vitamin C, Mg. per 100 Cc. | | | Values Below 0.5 Mg., % |
|---|---|---|---|---|
| | No. of Cases | Range | Average | |
| Acute rheumatic fever; unmodified diet | 30 | 0.11-0.68 | 0.30 | 97 |
| Acute rheumatic fever; modified diet* | 12 | 0.12-0.83 | 0.57 | 25 |
| Inactive rheumatic heart disease (adults and children) | 22 | 0.10-1.20 | 0.38 | 78 |
| Miscellaneous infections (children) | 92 | 0.08-1.29 | 0.48 | 59 |
| Miscellaneous noninfectious pathologic states (children) | 67 | 0.13-1.50 | 0.76 | 28 |
| Controls (tonsillectomy and adenoidectomy) | 19 | 0.22-1.57 | 0.81 | 26 |
| Tuberculosis (hospitalized children) | 110 | 0.09-1.55 | 0.79 | 25 |
| Tuberculosis (newly admitted children) | 6 | 0.11-1.21 | 0.81 | 33 |

* The individual plasma level and the dietary modification in each case were as follows:

| Patient | Cevitamic Acid, Mg. per 100 Cc. | Diet Modification |
|---|---|---|
| J. P. | 0.83 | Approximately 3 liters of orange juice during 4 days prior to analysis |
| W. B. | 0.62 | 500 cc. of tomato juice daily for past 3 weeks |
| W. | 0.82 | Approximately 1 liter of orange juice daily for 2 wk. prior to analysis |
| B. B. | 0.74 | Considerable increase in vitamin C intake during past month |
| M. W. | 0.71 | Orange juice, 750 cc. daily for 5 days prior to analysis |
| F. W. | 0.18 | Approximately 1 liter of orange juice daily for 1 wk. prior to analysis |
| G. B. | 0.12 | One month ago, 1 liter of tomato juice for about 2 weeks; then orange juice, 1 liter up to 1 week ago |
| O. N. | 0.48 | Orange juice or tomato juice, 250 cc. daily for past month |
| J. M. | 0.50 | Orange juice, approximately 200 cc. daily during past 5 months |
| B. | 0.65 | Orange juice, 2,500 cc. during 2½ days preceding test |
| P. K. | 0.61 | Increased vitamin C intake for past 3 weeks (since onset of present illness) |
| J. C. | 0.57 | High vitamin C diet for past 4 days |

children were of the same social status as those with rheumatic fever. Other control groups include ninety-two children with miscellaneous infections and sixty-seven patients with miscellaneous pathologic conditions unassociated with obvious infection (table 1). With few exceptions all determinations were made on blood samples taken with the subject in the fasting or postabsorptial state.

The patients with active rheumatic fever included thirty patients for whom no significant modification of the diet was known to have been made prior to the initial analysis. Twelve patients must be considered separately because a rather marked increase in the intake of vitamin C was instituted prior to the first plasma determination. A summary of the data relative to the several groups is given in table 1. It is seen that the vitamin C content of the blood was almost uniformly

lowered for patients with active rheumatic fever whose diet had not been significantly changed preceding the test. The average value for this group was 0.3 mg. per hundred cubic centimeters; 97 per cent showed values below 0.5 mg., which is considered the lower limit of "normal." These values lie in the range which Ingalls [15] said he considered indicates definite deficiency. This study adds support to the idea that infection per se acts to deplete the vitamin C reserve. However, the patients with nonrheumatic infection were not found to be depleted as uniformly or as strikingly as those with rheumatic fever, although in most instances the clinical evidence of active infection was more prominent.

A large group of tuberculous children who had been hospitalized for a few days to several years were available for study. Because they had been hospitalized and had received moderate or generous supplements of vitamin C, they were not entirely suitable as controls. However, the discovery that approximately 50 per cent of them showed a vitamin C value at or above 0.9 mg. per hundred cubic centimeters suggests that this is probably the optimal metabolic range for children. Of particular interest is the group of patients with chronic or inactive rheumatism. The average level for the twenty-two patients was 0.39 mg. Seventy-six per cent gave values below 0.5 mg. A subdivision of this group is of even greater interest. Eight rheumatic children, whom we had been following in the clinic for six months to three years, were examined during the spring of 1937. They showed no clinical evidence of an active rheumatic process. The respective vitamin C levels of the plasma were as follows: 0.18, 0.18, 0.14, 0.18, 0.1, 1.2, 0.45 and 0.24 mg. per hundred cubic centimeters. Only one of the entire group showed a satisfactory plasma value, and six of the eight showed values which were in the lowest ranges. This is the more remarkable in that these patients had been repeatedly urged to include liberal amounts of vitamin C in their diet. These data show that a high percentage of "rheumatic" patients, though not suffering from active disease, are in a potential if not an actual scorbutic state. It is obvious that any therapeutic study directed at estimation of the protective value of vitamin C against the onset or recurrence of rheumatic fever must be rigidly controlled.

It was possible to make one or more determinations of the vitamin C content of the plasma for nineteen of the patients with active rheumatic fever after the administration of liberal supplements of vitamin C. The results are shown graphically in chart 1. It will be seen that there are three general types of curves. Eight patients showed a relatively

15. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10**:577, 1937.

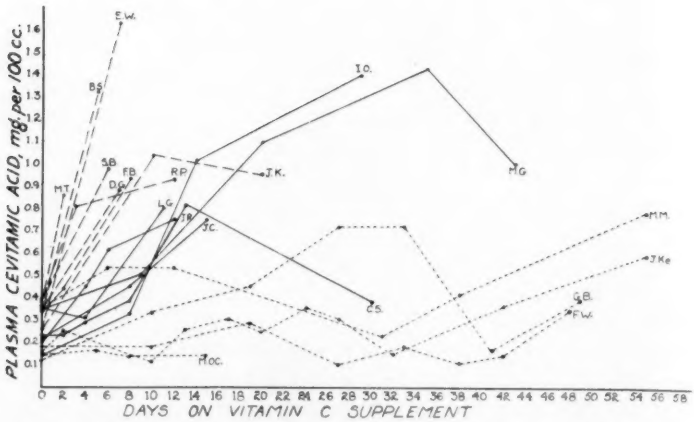


Chart 1.—Metabolism of vitamin C in rheumatic fever. Curves for patients with active rheumatic fever, showing the response of the blood plasma to the administration of vitamin C.

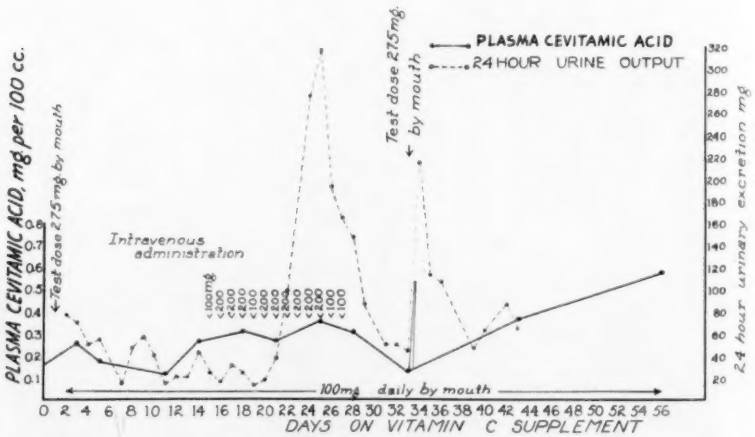
PLASMA CEVITAMIC ACID
24 HOUR URINE OUTPUT
PLASMA CEVITAMIC ACID, mg. per 100 cc.
24 hour urinary excretion mg.
Test dose 275 mg. by mouth
Test dose 275mg. by mouth
Intravenous administration
100mg. daily by mouth
DAYS ON VITAMIN C SUPPLEMENT

Chart 2.—Metabolism of vitamin C in rheumatic fever. Parallel curves of the cevitamic acid content of the plasma and of the twenty-four hour urinary excretion of cevitamic acid, illustrating the abnormal metabolism in a case of rheumatic fever.

prompt rise in the plasma value; six exhibited a rise but with a decided lag. Five exhibited an unexpected and as yet unexplained phenomenon in that they failed to show a satisfactory response even after prolonged and massive doses of the vitamin. One such case is of great interest:

J. Ke., a 15 year old boy, had the initial rheumatic injury of the heart six years before the present study was made. He entered the hospital with recurrent acute rheumatic fever associated with severe decompensation. In this instance we had the opportunity to make repeated estimations of the vitamin C content

TABLE 2.—*Daily Vitamin C Supplement in Cases Illustrated in Chart 1*

| Patient | Age, Years | Treatment, Days | Daily Supplement of Vitamin C |
|---|---|---|---|
| M. T. | 9 | 2 | Orange juice, 250 cc. |
| B. S. | 8 | 5 | Vitamin C, 100 mg. |
| E. W. | 9 | 7 | Orange juice, 500 cc. |
| R. P. | 14 | 12 | Orange juice, 500 cc. |
| D. G. | 5 | 7 | Vitamin C, 100 mg. |
| F. B. | 11 | 7 | Orange juice, 500 cc. |
| J. K. | 6 | 2 | Vitamin C, 200 mg. |
| | | 3-20 | Vitamin C, 150 mg. |
| S. B. | 5 | 6 | Vitamin C, 100 mg. |
| J. R. | 13 | 12 | Vitamin C, 150 mg. |
| M. G. | 13 | 44 | Orange juice, 500 cc. |
| L. G. | 8 | 11 | Orange juice, 500 cc. |
| J. C. | 8 | 15 | Orange juice, 500 cc. |
| I. O. | 13 | 29 | Vitamin C, 100 mg. |
| C. S. | 22 | 0 | Vitamin C, 550 mg. (test dose) |
| | | 2 | Vitamin C, 550 mg. (test dose) |
| | | 3 | Vitamin C, 50 mg. |
| | | 4-7 | Vitamin C, 100 mg. |
| | | 8-13 | Vitamin C, 200 mg. |
| | | 13-30 | At home; intake uncertain |
| G. B. | 21 | 14 | Vitamin C, 200 mg., and orange juice, 500 cc. |
| | | 15-18 | ? |
| | | 19-49 | Vitamin C, 200-250 mg. |
| M. M. | 11 | 55 | Orange juice, 500 cc. |
| | | 14-26 | Vitamin C, 150-200 mg., and orange juice |
| | | 31-55 | Vitamin C, 150 mg., and orange juice |
| M. O. | 12 | 4 | Vitamin C, 400 mg. (intravenous) |
| | | 4-7 | Orange juice |
| | | 7-15 | Vitamin C, 150 mg. |
| F. W. | 27 | 27 | Orange juice, 500-1,000 cc. |
| | | 28-48 | Vitamin C, 200 mg. (muscular), and 100 mg. (intravenous) |
| J. Ke. | 15 | 54 | High vitamin C (muscular) and (intravenous) (chart 2) |

of the plasma as well as of the urinary output (chart 2). The initial plasma level was 0.16 mg. per hundred cubic centimeters. After a moderate test dose, of 275 mg., of cevitamic acid, a relatively high urinary excretion (80 mg.) occurred in the subsequent twenty-four hours. After this he was given a daily oral supplement of 100 mg. of cevitamic acid. Two days after the test dose the plasma level was still severely lowered (0.26 mg.). In the ensuing eleven days the twenty-four hour urinary excretion of cevitamic acid ranged from 20 to 60 mg., although the plasma levels during fasting remained between 0.12 and 0.27 mg. per hundred cubic centimeters. At this time, in addition to the oral supplement of 100 mg., the daily intravenous administration of vitamin C was started, as indicated in the graph. For seven days the urinary output was lower than the preceding average, and the plasma level showed no significant change. However,

there was a remarkable improvement in the clinical condition of the patient within two days after the first intravenous injection of the sodium salt of cevitamic acid. The critical phase of cardiac decompensation had passed, and progressive improvement followed. This improvement was augmented later by diuresis induced with salyrgan. It is interesting that eventually a high urinary excretion occurred in spite of a persistently lowered vitamin C level of the blood. On the thirty-second day of illness a second oral test dose of 275 mg. of cevitamic acid was administered. Two hours later the cevitamic acid level of the plasma was 0.53 mg. per hundred cubic centimeters. The ensuing fifteen hour urinary output was high (220 mg.).

This record indicates that in certain cases of severe active rheumatic fever there may be a significant fault in the vitamin C metabolism. Although not conclusive, a record such as this suggests that the renal threshold for vitamin C may be abnormally lowered. Usually the plasma level and the urinary excretion are closely parallel,[16] although this type of reaction has been observed in a few cases.

## COMMENT

These data are in accord with our preliminary observation [14] and with the extensive study of Abbasy, Hill and Harris [11] and indicate a subsaturation or suboptimal nutritional state relative to vitamin C not only in active rheumatic fever but commonly in the interval or inactive phases of the disease. The three main possibilities which suggest themselves as the basis of this are, first, a deficient intake, second, depletion by the disease itself or by preceding infection and, third, an inherent or acquired metabolic fault. It is probable that one or more of these mechanisms may operate in a given case. The work of others that has been summarized here and our own studies, we feel, strongly support the concept that vitamin C deficiency may be an integral part of the mechanism in the pathogenesis of rheumatic fever. Prolonged, well controlled and carefully judged therapeutic and prophylactic studies appear to be indicated.

Although it is known that the vitamin C level of the blood plasma in normal and most pathologic states is an index of the intake of vitamin C and gives data comparable to the data based on urinary excretion, the full significance of the occasional occurrence of consistently lowered plasma levels in the face of a high intake of vitamin C is not known. No accurate data are available on the vitamin C content of connective tissue. It is possible that the latter is dependent on an adequate concentration in the blood for normal metabolism. Lowered cevitamic acid levels of the blood are obviously not solely found in rheumatic fever or rheumatoid arthritis, and in individual cases they do not denote scurvy. The latter is a tissue change resulting from the operation of suboptimal

16. Greenberg, Rinehart and Phatak.[13] Rinehart, Greenberg and Christie.[14]

or low metabolic levels over some period of time. However, the finding of practically uniformly lowered vitamin C levels in the blood in rheumatic fever, not only in the active but commonly in the quiescent phases of the disease, together with other accumulated evidence cited, strongly suggests that vitamin C deficiency exists in this disease and is of etiologic significance.

## SUMMARY AND CONCLUSIONS

The cevitamic acid content of the blood plasma is practically uniformly low for patients with acute rheumatic fever if a significantly high increase in the intake of vitamin C has not been made preceding the determination. Furthermore, the majority of patients convalescent from rheumatic fever or with inactive rheumatic fever also show low blood plasma values. This study is in accord with that of Abbasy, Hill and Harris,[11] which was based on urinary excretion of vitamin C. Observations are cited indicating that a fundamental fault in metabolism of vitamin C exists in some cases of acute rheumatic fever. These data indicate that vitamin C deficiency commonly exists in rheumatic fever, and they add support to the concept that this deficiency may be of etiologic significance in the disease. Prolonged and carefully controlled prophylactic and therapeutic studies are indicated.

# COMPLEMENT FIXATION IN AMEBIASIS

## A COMPARATIVE EVALUATION IN CLINICAL PRACTICE

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The first reference to the serologic diagnosis of amebiasis was made by Izar,[1] in 1914. He experimented with complement fixation, the technic on which the Wassermann reaction for the diagnosis of syphilis is based. While sporadic studies were subsequently made, it remained for Craig [2] (1927) to place this test on a relatively practical basis by improving the preparation of the antigen and standardizing the technic. Later attempts to improve the Craig test resulted in minor changes by Sherwood and Heathman [3] (1932), Weiss and Arnold [4] (1934) and Tsuchiya [5] (1934). Each of these workers or pair of workers with a different modification of the test has corroborated, in the main, Craig's contention of the specificity of complement fixation in the diagnosis of amebiasis. Details of the history and development of this procedure have been treated adequately in Craig's [6] excellent monograph entitled "Amebiasis and Amebic Dysentery" (1934).

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From the Gastro-Intestinal Section of the Medical Clinic of the Johns Hopkins Hospital and Medical School and the Department of Protozoölogy, the Johns Hopkins School of Hygiene and Public Health.

1. Izar, G.: Ueber das Vorkommen spezifischer Antikörper im Serum von Amöbenruhrkranken (Entamoeba tetragena), (supp.) Arch. f. Schiffs- u. Tropenhyg. **18**:36-39, 1914.

2. Craig, Charles F.: Observations upon the Hemolytic, Cytolytic and Complement-Binding Properties of Extracts of Endamoeba histolytica, Am. J. Trop. Med. **7**:225-240, 1927.

3. Sherwood, N. P., and Heathman, L.: Further Studies on the Antigenic Properties of Pathogenic and Free Living Amebas: Complement Fixation Tests in Amebic Dysentery, Am. J. Hyg. **16**:124-136, 1932.

4. Weiss, E., and Arnold, L.: Complement Fixation Test for Amebiasis, Am. J. Digest. Dis. & Nutrition **1**:231-233, 1934; The Specificity of the Complement Fixation Test for Amebiasis, ibid. **1**:548-552, 1934.

5. Tsuchiya, H.: Further Studies on the Cultivation of Endameba Histolytica and a Complement Fixation Test for Amebiasis, J. Lab. & Clin. Med. **19**:495-504, 1934.

6. Craig, C. F.: Amebiasis and Amebic Dysentery, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

Interest in amebiasis has greatly increased in recent years, especially since the epidemic in Chicago in 1933. Clinicians and workers in diagnostic laboratories have been desirous of making use of serologic methods the general principles and technic of which are familiar to them. Thus far no objective evaluation of complement fixation in amebiasis as it is employed at present in clinical practice has appeared. The present report presents and analyzes some data in this regard statistically.

## PURPOSE

Heretofore practically all the work on complement fixation in amebiasis has been carried on by the originator of the improved method and by the proponents of the several modifications. It was our desire to test this procedure as a diagnostic aid in clinical practice. To this end and in order to avoid all possible bias, a cooperative investigation was undertaken by an internist, whose major interests lay in digestive diseases, a protozoologist and 3 serologists. Two of the serologists had no direct connection with the founding of the test or of its modifications. The protozoologist and the serologists were never acquainted with each other's results, and the character of each case was not divulged to them until the completion of the study. The cases investigated, with rare exceptions,[7] called for extensive studies of the digestive tract, including special examinations of the stools. It is in this particular type of case that information derived from the complement fixation test would be most valuable to the clinician.

## MATERIAL AND METHODS

*Material.*—The clinical material on which this study is based consisted of 14 persons without symptoms and 136 hospital and private patients exhibiting some abdominal symptoms. All these persons were grouped according to the disorder presented or other criteria, as follows:

Chronic Ulcerative Colitis: The patients with this disorder presented involvement of the large intestine, regional or general, including the rectum, which resulted in a sanguineous, mucosanguineous or mucopurulent exudate, with or without diarrhea, and which was due to unknown or undemonstrable factors. Those from whom Endamoeba histolytica was isolated but in whom specific amebicidal therapy resulted in eradication of the parasite without the obtaining of complete subjective and objective relief were regarded as having ulcerative colitis and not amebic dysentery.

Amebic Dysentery: The patients with this disorder presented blood and pus in the dejecta from which E. histolytica was isolated and responded completely—subjectively and objectively—to specific amebicidal therapy.

Bacillary Dysentery: The patients with this disorder showed the dysenteric syndrome without the presence of E. histolytica, and from them the Flexner bacillus was isolated.

7. Fourteen passers of Endamoeba histolytica cysts who appeared to be in good health were encountered during protozoologic surveys and were included in this study.

Indeterminate Dysentery: The patients with this disorder showed the dysenteric syndrome, but the site or cause of involvement could not be demonstrated.

Chronic Diarrhea: The patients with this disorder had ill formed, relatively frequent bowel movements, without blood and pus.

Disorders Marked by Varied Abdominal Symptoms: The patients with these disorders presented long-standing, frequently indefinite and heretofore undetermined abdominal symptoms, which were sufficiently annoying or severe to cause them to seek and to permit intensive study, which were not characteristic of the aforementioned conditions and for which no causative organic disease could be found. There were 4 exceptions: Later, 3 of the patients were discovered to have intestinal malignant growths, and 1 typhoid. The chief complaints were those of pyrosis, eructation, flatulence, distention, constipation, constipation together with a rare tendency to loose but not frequent stools, borborygmus, generalized abdominal discomfort, abdominal pain which varied as to location and severity from time to time, easy fatigability and a feeling of being "just below par." By some these complaints have been classified as indicating psychoneurosis. Craig has reported similar symptoms as being due to E. histolytica.

Healthy Carriers: The healthy carriers were a group of young men and women without any symptoms in whom cysts of E. histolytica were encountered during protozoologic surveys and in whom immediately subsequent complete clinical examinations revealed no organic disease.

No Diagnosis: There was no opportunity given for clinical investigation in some instances, and no diagnosis was made, but cysts of E. histolytica were encountered during a protozoologic survey.

*Fecal Examinations.*—Dejecta were submitted to the protozoologist for immediate examination, usually promptly after defecation. The number of examinations recorded in table 1 indicates those made by him. The protozoologic diagnoses shown are solely his own. In certain instances material was taken directly from the site of involvement through the rectosigmoidoscope and was examined at once. Smears stained with iron hematoxylin and cultures in the Tanabe-Chiba and Cleveland-Collier mediums were frequently prepared from this material by one of us (Dr. Paulson). The iron-hematoxylin preparations and questionable cultures were observed also by the protozoologist. In practically all instances more examinations of stools were made than is indicated by table 1, since frequent observations by house officers and technicians have been disregarded because it was not desired to assume responsibility for their work.

*Serologic Examinations.*—Serums were sent to one or more of three laboratories,[8] herein designated as A, B and C. Laboratory A had at different intervals the Craig, Sherwood-Heathman and Arnold antigens. Laboratory B had only the Craig antigen, and laboratory C, an Arnold antigen. Laboratories B and C prepared their own antigens. Samples of serums were mailed to the second and third laboratories. The technic employed with each antigen was that outlined by the investigator whose name is associated with the antigen. These details have been adequately described in original papers and reviewed by Craig.[6]

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8. Laboratory A was the Albert Keidel-Joseph Earle Moore Laboratory, Baltimore. For use in this laboratory Drs. Sherwood and Arnold kindly submitted their own antigens, and Capt. Williams sent a Craig antigen made in the Army Medical School. Laboratory B was the Serologic Laboratory (in charge of Capt. W. C. Williams) of the Army Medical School, Washington, D. C. Laboratory C was the Department of Pathology and Bacteriology (Prof. Lloyd Arnold in charge) at the College of Medicine, University of Illinois, Chicago.

TABLE 1.—*Clinical Diagnosis, Reports of Complement Fixation and Parasitologic Findings*

| Case No. | Diagnosis | Complement Fixation* | | | | | Stools Examined Before Therapy |
|---|---|---|---|---|---|---|---|
| | | Laboratory A | | | Laboratory B | Laboratory C | |
| | | Arnold Antigen | Sherwood Antigen | Craig Antigen | Craig Antigen | Arnold Antigen | |
| | **A. At Least One Complement Fixation Test Showed a Positive reaction** | | | | | | |
| | **1. E. Histolytica Found** | | | | | | |
| 1 | Amebic dysentery | .. | 4+ | 4+ | Strongly positive | ... | 1† |
| 2 | Amebic dysentery | .. | .. | — | Weakly positive (50%) | ... | 1† |
| 3 | Amebic dysentery | .. | — | — | 50%+ | ... | 2 |
| 4 | Amebic dysentery | .. | — | — | — | 3+ | 1 |
| | 2½ mo. later | .. | .. | .. | — | 4+ | .. |
| 5 | Amebic dysentery | .. | — | — | — | 4+ | 1 |
| 6 | Amebic dysentery | .. | — | — | — | 4+ | 2 |
| 7 | Amebic dysentery | .. | — | — | 50-60%+ | 3+ | 1 |
| 8 | Amebic dysentery | .. | 4+ | 4+ | Strongly positive | 4+ | 1 |
| | 2½ mo. later‡ | .. | 4+ | .. | Strongly positive | 4+ | 3 |
| 9 | Amebic dysentery | .. | — | — | — | 4+ | 2 |
| 10 | Amebic dysentery | .. | — | — | — | 4+ | 1§ |
| 11 | Amebic dysentery | .. | 4+ | 4+ | Strongly positive | ... | 1 |
| 12 | Amebic dysentery | .. | 2+ | 2+ | Weakly positive | ... | 3 |
| 13 | Amebic dysentery | .. | Anti-complementary | Anti-complementary | Strongly positive | ... | 4 |
| 14 | Amebic dysentery | .. | .. | .. | ..... | 4+ | 1 |
| 15 | Varied abdominal symptoms | .. | .. | — | Strongly positive 2+ | ... | 1 |
| 16 | Varied abdominal symptoms | .. | .. | .. | Weakly positive | ... | 1 |
| 17 | Varied abdominal symptoms | .. | .. | — | Weakly positive (50%) | ... | 1 |
| | 5 mo. later‖ | .. | .. | .. | — | ... | 3 |
| 18 | Varied abdominal symptoms | .. | .. | 4+ | Weakly positive | ... | 1 |
| 19 | Varied abdominal symptoms | .. | .. | — | Doubtful (±) | ... | 1 |
| 20 | Varied abdominal symptoms | .. | — | — | Weakly positive (50%) | ... | 1 |
| 21 | Varied abdominal symptoms | .. | — | .. | Weakly positive (50%) | ... | 1 |
| 22 | Varied abdominal symptoms | .. | .. | — | Weakly positive (60%) | ... | 1 |
| 23 | Healthy carrier | .. | .. | .. | Strongly positive | ... | 2 |
| | 3 mo. later‖ | .. | .. | .. | — | ... | 3 |
| | 6 mo. later‖ | .. | .. | .. | Strongly positive | ... | 3 |
| 24 | Healthy carrier | .. | .. | .. | — | 4+ | 1 |
| 25 | Healthy carrier | .. | .. | .. | ..... | 4+ | 1 |
| 26 | Ulcerative colitis | .. | .. | 2+ | 4+ | ... | 10† |
| 27 | Ulcerative colitis | .. | .. | 1+ | — | ... | 2 |
| 28 | Chronic diarrhea | .. | .. | — | Doubtful + | ... | 5† |
| 29 | Chronic diarrhea | .. | 0.1 = 3+ 0.05 = 2+ 0.025 = 1+ | — | Anticomplementary | 4+ | 1§ |
| 30 | Chronic diarrhea | .. | .. | .. | ..... | 3+ | 1 |
| | **2. E. Histolytica Not Found** | | | | | | |
| 31 | Chronic diarrhea | .. | 2+ | 1+ | — | ... | 1† |
| 32 | Chronic diarrhea | .. | .. | .. | Strongly positive | ... | 1 |
| 33 | Chronic diarrhea | .. | .. | — | Doubtful (50%) | ... | 1 |
| 34 | Chronic diarrhea | .. | .. | 0.1 = 2+ 0.05 = 2+ 0.025 = 1+ | Doubtful | ... | 1 |
| 35 | Chronic diarrhea | .. | .. | — | Strongly positive | ... | 6† |
| | 2 mo. later | .. | .. | — | — | ... | 3 |
| | 3 mo. later | .. | .. | — | Anticomplementary | ... | 3 |
| 36 | Chronic diarrhea | .. | .. | 0.1 = anti-complementary 0.05 = 4+ | — | ... | 1 |
| 37 | Chronic diarrhea | .. | — | — | — | 4+ | 4† |
| 38 | Chronic diarrhea | .. | .. | .. | Strongly positive | ... | 3† |
| 39 | Ulcerative colitis¶ | — | .. | .. | — | 4+ | 6† |
| 40 | Ulcerative colitis | .. | .. | .. | ..... | 2+ | 1† |
| 41 | Ulcerative colitis | .. | — | — | — | 3+ | 2† |
| 42 | Ulcerative colitis | .. | .. | .. | 4+ | ... | 4† |
| | 4 mo. later | .. | .. | .. | 4+ | ... | 3 |
| 43 | Ulcerative colitis | .. | 0.1 = 4+ 0.05 = 4+ 0.025 = 4+ | 0.05 = 1+ 0.025 = — | — | ... | 1 |
| 44 | Ulcerative colitis# | — | .. | .. | — | — | 3 |
| | 16 days later | — | .. | .. | .. | ... | 3 |
| | 18 days later | — | .. | .. | .. | 4+ | 3 |
| 45 | Ulcerative colitis | .. | — | — | Very weakly positive | ... | 1 |
| 46 | Ulcerative colitis | .. | .. | — | Weakly positive | ... | 5† |
| 47 | Ulcerative colitis# | .. | 4+ | 2+ | — | 2+ | 1† |

TABLE 1.—*Clinical Diagnosis, Reports of Complement Fixation and Parasitologic Findings—Continued*

| Case No. | Diagnosis | Complement Fixation* | | | | | Stools Examined Before Therapy |
|---|---|---|---|---|---|---|---|
| | | Laboratory A | | | Laboratory B | Laboratory C | |
| | | Arnold Antigen | Sherwood Antigen | Craig Antigen | Craig Antigen | Arnold Antigen | |
| 48 | Varied abdominal symptoms | .. | .. | .. | Doubtful | ... | 4† |
| 49 | Varied abdominal symptoms** | — | .. | .. | ..... | 4+ | 2† |
| 50 | Varied abdominal symptoms | .. | .. | .. | ..... | 2+ | 2† |
| 51 | Varied abdominal symptoms†† | .. | .. | .. | Weakly positive | ... | 1 |
| 52 | Bacillary dysentery** | .. | .. | — | 80-85%+ | ... | 7† |
| 53 | Indeterminate type of dysentery¶ | .. | .. | .. | Weakly positive | ... | 7† |
| | B. Negative Reaction to Complement Fixation Test | | | | | | |
| | 1. E. Histolytica Found | | | | | | |
| 54 | Varied abdominal symptoms | — | .. | .. | ..... | ... | 2 |
| 55 | Varied abdominal symptoms | .. | .. | Anticomplementary | — | ... | 1 |
| 56 | Varied abdominal symptoms | .. | .. | .. | — | ... | 2 |
| 57 | Varied abdominal symptoms | .. | .. | .. | — | ... | 1 |
| 58 | Varied abdominal symptoms | .. | .. | .. | — | ... | 1 |
| 59 | Varied abdominal symptoms | .. | .. | — | — | ... | 1 |
| 60 | Varied abdominal symptoms | .. | .. | — | — | ... | 1 |
| 61 | Varied abdominal symptoms | .. | .. | .. | — | — | 1† |
| 62 | Varied abdominal symptoms | .. | .. | — | — | ... | 1 |
| 63 | Varied abdominal symptoms‡‡ | — | .. | .. | ..... | ... | 2 |
| 64 | Varied abdominal symptoms | — | .. | .. | — | — | 3 |
| 65 | No diagnosis | .. | .. | — | — | ... | 3 |
| 66 | No diagnosis | .. | .. | — | — | ... | 3 |
| 67 | No diagnosis | .. | .. | — | — | ... | 3 |
| 68 | No diagnosis | .. | .. | — | — | ... | 3 |
| 69 | No diagnosis | .. | — | .. | — | ... | 3 |
| 70 | Healthy carrier | .. | .. | .. | — | ... | 2† |
| 71 | Healthy carrier | .. | .. | .. | — | ... | 1† |
| 72 | Healthy carrier | .. | .. | .. | — | ... | 1† |
| 73 | Healthy carrier | .. | .. | .. | — | ... | 2† |
| 74 | Healthy carrier | .. | .. | — | — | ... | 1† |
| 75 | Healthy carrier | — | .. | .. | ..... | ... | 1 |
| 76 | Amebic dysentery | — | .. | .. | — | — | 3 |
| 77 | Amebic dysentery | — | .. | .. | ..... | ... | 3 |
| 78 | Amebic dysentery | .. | .. | — | — | ... | 2 |
| | 2½ mo. later‡ | .. | — | — | ..... | ... | 3 |
| 79 | Amebic dysentery | .. | .. | — | — | ... | 7†§§ |
| 80 | Amebic dysentery** | .. | .. | .. | ..... | — | 2 |
| 81 | Amebic dysentery | .. | .. | — | — | ... | 1 |
| 82 | Amebic dysentery | .. | .. | .. | ..... | — | 1¶¶ |
| 83 | Ulcerative colitis# | .. | .. | .. | — | ... | 1 |
| 84 | Ulcerative colitis | — | .. | .. | ..... | ... | 3† |
| | 6 mo. later‖ | — | .. | .. | ..... | ... | 3 |
| 85 | Chronic diarrhea | — | .. | .. | — | ... | 1 |
| | 2 mo. later‖ | .. | .. | .. | — | ... | 3 |
| 86 | Chronic diarrhea | — | .. | — | ..... | — | 2 |
| 87 | Chronic diarrhea | .. | .. | — | — | ... | 3 |
| | 2. E. Histolytica Not Found | | | | | | |
| 88 | Chronic diarrhea | .. | .. | — | — | ... | 2† |
| 89 | Chronic diarrhea | .. | .. | — | — | ... | 3† |
| 90 | Chronic diarrhea | .. | .. | — | — | ... | 2† |
| 91 | Chronic diarrhea | .. | — | — | ..... | ... | 1† |
| 92 | Chronic diarrhea | .. | .. | . | — | ... | 2† |
| 93 | Chronic diarrhea | .. | .. | — | — | ... | 2 |
| 94 | Chronic diarrhea | .. | .. | .. | — | ... | 5 |
| 95 | Chronic diarrhea | .. | .. | — | — | ... | 1† |
| 96 | Chronic diarrhea** | .. | .. | — | — | ... | 2† |
| 97 | Chronic diarrhea | .. | .. | — | — | ... | 1† |
| 98 | Chronic diarrhea | .. | .. | — | — | ... | 1 |
| 99 | Chronic diarrhea | .. | .. | Anticomplementary | — | ... | 2† |
| 100 | Chronic diarrhea | .. | .. | — | — | ... | 1 |
| 101 | Chronic diarrhea | .. | .. | .. | ..... | — | 1 |
| 102 | Chronic diarrhea | — | .. | .. | ..... | ... | 2† |
| 103 | Chronic diarrhea | — | .. | .. | ..... | ... | 3† |

TABLE 1.—*Clinical Diagnosis, Reports of Complement Fixation and Parasitologic Findings—Continued*

| Case No. | Diagnosis | Complement Fixation* | | | | | Stools Examined Before Therapy |
|---|---|---|---|---|---|---|---|
| | | Laboratory A | | | Laboratory B | Laboratory C | |
| | | Arnold Antigen | Sherwood Antigen | Craig Antigen | Craig Antigen | Arnold Antigen | |
| 104 | Chronic diarrhea | — | .. | .. | ..... | ... | 2† |
| 105 | Chronic diarrhea | — | .. | .. | ..... | ... | 2 |
| 106 | Chronic diarrhea | — | .. | .. | ..... | ... | 1† |
| 107 | Varied abdominal symptoms | — | .. | .. | ..... | — | 1 |
| 108 | Varied abdominal symptoms‡‡ | — | .. | .. | — | ... | 1 |
| 109 | Varied abdominal symptoms | .. | — | — | — | ... | 2 |
| 110 | Varied abdominal symptoms | .. | .. | — | — | ... | 2 |
| 111 | Varied abdominal symptoms | .. | .. | Anticomplementary | — | ... | 1 |
| 112 | Varied abdominal symptoms | .. | .. | — | — | ... | 2† |
| 113 | Varied abdominal symptoms | .. | .. | — | — | ... | 2† |
| 114 | Varied abdominal symptoms | .. | — | — | — | — | 1 |
| 115 | Varied abdominal symptoms | .. | — | — | — | — | 1 |
| 116 | Varied abdominal symptoms | .. | — | — | — | — | 1 |
| 117 | Varied abdominal symptoms | .. | .. | .. | — | — | 2 |
| 118 | Varied abdominal symptoms | .. | .. | .. | — | — | 3 |
| 119 | Varied abdominal symptoms | — | .. | .. | ..... | ... | 1 |
| 120 | Varied abdominal symptoms | — | .. | .. | ..... | ... | 2† |
| 121 | Varied abdominal symptoms | — | .. | .. | ..... | ... | 2† |
| 122 | Varied abdominal symptoms | — | .. | .. | ..... | ... | 2† |
| 123 | Varied abdominal symptoms | — | .. | .. | ..... | ... | 1 |
| 124 | Varied abdominal symptoms‡‡ | .. | .. | — | — | ... | 1 |
| 125 | Varied abdominal symptoms | .. | .. | .. | ..... | — | 1 |
| 126 | Ulcerative colitis | .. | .. | .. | ..... | — | 1 |
| 127 | Ulcerative colitis | .. | .. | .. | — | ... | 1† |
| 128 | Ulcerative colitis | .. | .. | — | — | ... | 4† |
| 129 | Ulcerative colitis | .. | .. | — | — | ... | 4 |
| 130 | Ulcerative colitis# | .. | .. | — | — | ... | 3 |
| 131 | Ulcerative colitis | .. | .. | — | — | ... | 1† |
| 132 | Ulcerative colitis | .. | .. | — | — | ... | 2† |
| 133 | Ulcerative colitis | .. | .. | — | — | ... | 4† |
| 134 | Ulcerative colitis# | .. | .. | .. | — | — | 3 |
| 135 | Ulcerative colitis# | .. | .. | .. | ..... | — | 1† |
| 136 | Ulcerative colitis | — | .. | .. | ..... | ... | 3† |
| 137 | Ulcerative colitis | — | .. | .. | ..... | ... | 4† |
| 138 | Ulcerative colitis | — | .. | .. | ..... | ... | 8† |
| 139 | Ulcerative colitis | — | .. | .. | ..... | ... | 1† |
| 140 | Ulcerative colitis | — | .. | .. | ..... | ... | 4† |
| 141 | Ulcerative colitis | — | .. | .. | ..... | ... | 3 |
| 142 | Ulcerative colitis | — | .. | .. | ..... | ... | 4† |
| 143 | Ulcerative colitis | .. | .. | .. | — | ... | 3† |
| 144 | Ulcerative colitis | .. | — | — | — | ... | 1† |
| 145 | Ulcerative colitis | .. | — | — | — | ... | 1† |
| 146 | Ulcerative colitis | — | .. | .. | ..... | ... | 4† |
| 147 | Bacillary dysentery** | .. | .. | — | — | ... | 6 |
| 148 | Bacillary dysentery** | .. | .. | — | — | ... | 2 |
| 149 | Bacillary dysentery** | — | .. | .. | ..... | ... | 2 |
| 150 | Bacillary dysentery** | .. | .. | .. | — | ... | 2† |

* The decimal numbers represent the fraction of a cubic centimeter of antigen employed.

† Coproculture on Cleveland-Collier and on Tanabe-Chiba medium; smears stained with iron and hematoxylin.

‡ E. histolytica was not found at this time, although the organism was present one month before.

§ Coproculture on Cleveland-Collier and on Tanabe-Chiba medium.

‖ E. histolytica not found at this time.

¶ With ileitis.

# Associated with lymphogranuloma venereum.

** Eberthella paradysenteriae (Flexner) isolated from feces.

†† Condition later diagnosed as typhoid.

‡‡ Intestinal malignant growth.

§§ Microscopic examinations were complicated by the presence of barium sulfate (Andrews, J., and Paulson, M.: Am. J. M. Sc. **181**: 102-106, 1931).

‖‖ Smears stained with iron hematoxylin.

In the beginning it was planned in each case to obtain a series of multiple serologic reports based on different antigens. This design was frustrated by the shortage of antigens and serums, by the contamination and anticomplementary action of certain serums and occasionally by the nonreceipt of serologic reports.

## RESULTS

*General Data.*—The results of the clinical, serologic and parasitologic examinations in the 150 individual cases are shown in table 1 and

TABLE 2.—*Comparison of All Serologic and Parasitologic Findings in Various Clinical Groups*

| Clinical Diagnosis | Number of Cases | E. histolytica Found by Microscopic Examination, Percentage | Complement Fixation | | | Positive by Both Complement Fixation (All Positive) and Microscopic Examination, Percentage | Probability per 100 Times of Same Combination by Chance |
|---|---|---|---|---|---|---|---|
| | | | Weakly Positive, Percentage | Strongly Positive, Percentage | All Positive, Percentage | | |
| A. Known symptoms | | | | | | | |
| Amebic dysentery | 21 | 100.0 | 14.3 | 52.4 | 66.7 | 66.7 | |
| Chronic diarrhea | 33 | 18.2 | .... | .... | 33.2 | 9.1 | 33.0 |
| E. histolytica found | 6 | .... | 16.7 | 33.3 | 50.0 | | |
| E. histolytica not found | 27 | .... | 11.1 | 18.5 | 29.6 | | |
| Varied abdominal symptoms | 42 | 45.2 | .... | .... | 28.6 | 19.0 | 7.0 |
| E. histolytica found | 19 | .... | 31.6 | 10.5 | 42.1 | | |
| E. histolytica not found | 23 | .... | 13.0 | 4.4 | 17.4 | | |
| Ulcerative colitis | 34 | 11.8 | .... | .... | 32.4 | 5.9 | 42.0 |
| E. histolytica found | 4 | .... | 25.0 | 25.0 | 50.0 | | |
| E. histolytica not found | 30 | .... | 10.0 | 20.0 | 30.0 | | |
| Bacillary and indeterminate dysentery, E. histolytica not found | 6 | 0.0 | 16.7 | 16.7 | 33.7 | | |
| Subtotal | 136 | 36.8 | 15.4 | 21.3 | 36.8 | 19.9 | 0.1 |
| E. histolytica found | 50 | .... | 22.0 | 32.0 | 54.0 | | |
| E. histolytica not found | 86 | .... | 11.6 | 15.1 | 26.7 | | |
| B. No symptoms | | | | | | | |
| Healthy carriers | 9 | 100.0 | 0.0 | 33.3 | 33.3 | | |
| No diagnosis* | | | | | | | |
| E. histolytica found | 5 | 100.0 | 0.0 | 0.0 | 0.0 | | |
| Subtotal | 14 | 100.0 | 0.0 | 21.4 | 21.4 | | |
| Total | 150 | 42.7 | 14.0 | 21.3 | 35.3 | 20.0 | 1.0 |
| E. histolytica found | 64 | .... | 17.2 | 29.7 | 46.9 | | |
| E. histolytica not found | 86 | .... | 11.6 | 15.1 | 26.7 | | |

* These patients were encountered during a protozoologic survey of convicts in a local penitentiary. They were not examined clinically but had not complained of ill health.

are summarized in table 2. For the 163 serums submitted for examination there were reports based on a single antigen in 70 cases, based on two antigens or from two laboratories in 62 cases, based on three antigens or from three laboratories in 19 cases and based on four antigens in 12 cases.

The average number of fecal examinations made in the cases in which positive results were obtained was 1.5; in the cases in which E. histolytica was not found, 2.5. As indicated in table 1, many of the examinations of fresh stools were supplemented by the inspection of smears treated with iron hematoxylin and by attempts to demonstrate the organism in either the Cleveland-Collier or the Tanabe-Chiba medium. The observations on stained smears added nothing to the results of examination of fresh material but were frequently of confirmatory interest. In 4 cases E. histolytica was first seen on the Tanabe-Chiba medium; in 2 of these cases there was growth on the other culture medium also. Even an approximation of efficiency in detecting E. histolytica in the present series can hardly be ventured. Some of the stools submitted were formed, thereby reducing the diagnostic efficiency. Others were loose, owing either to the nature of the patient's disorder or to the fact that a purge had been given in order to increase the likelihood of finding protozoa in the stools.[9] Thus, it is to be emphasized in this as in other similar studies that while positive results of microscopic examinations for E. histolytica are relatively dependable, the same degree of reliability cannot be attached when organisms are not found.

Partially positive reactions, to the complement fixation test, i. e., weak, doubtful, 1+ or 2+ or a fixation of less than 75 per cent, are shown separately in tables 1 and 2, as it was subsequently found that the inclusion or exclusion of these instances in which there was a positive reaction modified the efficiency of the serologic tests in a marked though varied manner.

*Comparison of Laboratory Findings in Clinical Groups.*—When the individual patients were combined into clinically similar groups, as, for example, those with chronic diarrhea, and when the positive diagnoses with all serologic systems were used (table 2), the groups of those in whom E. histolytica was found regularly showed higher ratios of positive results than did those in whom E. histolytica was not found. In no group or fraction of a group did it closely approach 100 per cent, and in all groups a positive reaction was reported for a number of patients in whom E. histolytica was not found. The differences in the ratios of the positive results for the various groups are not significant, owing primarly to the small numbers involved. For the total number of persons examined, however, the difference is significant, and when only patients with known symptoms of amebiasis are considered it is more highly significant, indicating that complement fixation is more successful in apprehending symptomatic than nonsymptomatic amebiasis.

9. Andrews, Justin: The Diagnosis of Intestinal Protozoa From Purged and Normally-Passed Stools, J. Parasitol. **20**:253-254, 1934.

An attempt to evaluate more critically the laboratory results with respect to the various clinical entities was made by applying the chi-square test to fourfold tables showing the association of cases in which E. histolytica was found with those cases in which complement fixation was positive. For this purpose the results obtained with all antigens in all laboratories were used, and partially positive results were considered as positive. As shown in table 3, this procedure gave more significant results when applied to the combined serologic data than when only strongly positive reactions were read as positive. The object was to determine for each clinical group the number of times in 100 that similar combinations of positive and negative results regarding the two attributes might be due to chance alone. The greater the probability of random assortment, the less likely it becomes that the indicated association of the attributes is meaningful and significant. The determination of the point at which purely accidental distribution stops and significant relationship begins is an arbitrary one. Most statisticians consider a probability of 4 or 5 times in 100 (i. e., equivalent to a chi-square of 4, or a difference of twice its own standard deviation) to be a practical limit to the significant concurrence of two attributes. Thus if they may occur together by sheer chance more frequently than 4 or 5 times in 100, there is little likelihood that they are significantly related, whereas if their association is shown to be one which might happen by chance less than 4 or 5 times in 100, the assumption of a significant relation is usually justified.

The data on amebic dysentery in this series are not susceptible to this type of statistical analysis, as there was deliberate selection in respect to the presence of E. histolytica. No dysentery was termed amebic unless organisms were found. One patient came to our attention early in the course of the disorder, and possibly the serologic tests (with negative results) were made before specific antibodies had had an opportunity to develop. This may have been the case in other instances.

In none of the other three clinical groups of patients tested does the association of positive serologic and parasitologic findings appear to be significant on the basis of the small numbers involved. Nevertheless, the computed probabilities of similar assortments by chance show that positive complement fixation reactions are less likely to have a fortuitous distribution with respect to the finding of E. histolytica in the case of "varied abdominal symptoms" than with either "chronic diarrhea" or "ulcerative colitis." Unless many amebic infections were not recognized parasitologically, this shows a strong tendency for falsely positive reactions to occur in ulcerative colitis, an observation which

has already been made by Sherwood and Heathman,[3] Kiefer[10] and Craig,[11] and suggests that the same may be true with regard to chronic diarrhea. It is in cases of these conditions that serologic information might be most helpful to the clinician. However, all persons studied being taken as one group, the association of positive attributes is significant, and, as indicated previously, when the group is restricted to patients with abdominal symptoms, it is even more highly significant.

*Comparison of Various Technics of Complement Fixation.*—From the standpoint of general agreement of reports on the same antigen even in different hands, the results showed remarkable correspondence when it is considered that the antigens of the same type used in different laboratories may not have been of the same lot or of the same age. The Craig antigens reacting with the same serums in laboratories A and B agreed in 73.6 per cent of the 72 cases when partially positive reactions were regarded as positive and in 91.7 per cent when partially positive reactions were considered negative. Only 8 serums were tested with Arnold antigen in laboratories A and C. Five of these were reported as showing a negative reaction by both serologists; 3 were reported as showing a 4 + reaction in laboratory C and a negative reaction in laboratory A.

The results obtained with the Craig antigen compared favorably with those obtained with the Sherwood antigen in laboratory A. Of 29 serums tested with both, 96.6 per cent agreed when partially positive reactions were listed as positive and 89.7 per cent when they were called negative.

The Arnold antigen in laboratory C gave results which were least conformable with those based on the other antigens. Compared with the reactions obtained with the Craig antigen in laboratory B, only 54.2 per cent of the reactions agreed irrespective of how the partially positive reactions were classified.

In comparison of multiple examinations with similar or different antigens the following results were obtained: Two reports were available in each of 62 cases. With partially positive reactions considered as positive, 69.4 per cent of the reports agreed; with partial reactions considered as negative, 83.9 per cent agreed. In the 19 instances in which three reports for each were obtained, 68.4 per cent of the reports were in agreement when the partially positive reactions were considered positive and 84.2 per cent when they were classified as negative.

10. Kiefer, E. D.: The Craig Complement-Fixation Test for Amebiasis in Chronic Ulcerative Colitis, Am. J. M. Sc. **183**:624-631, 1932.

11. Craig, C. F.: Further Observations upon the Complement Fixation Test in the Diagnosis of Amebiasis, J. Lab. & Clin. Med. **18**:873-881, 1933.

Reports based on four antigens were forthcoming in each of 12 cases, and 33.3 per cent agreed irrespective of the manner in which the doubtful results were listed.

From these considerations it appears that the complement fixation test in different hands and with different antigens gave moderately comparable results, with the exception of those reported with the Arnold antigen in laboratory C. As a general rule, greater correspondence of results was secured by grouping partially positive reactions with negative reactions.

TABLE 3.—*Comparison of Results of Various Methods of Complement Fixation*

| | | | Complement Fixation | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Strong Positive Reactions | | | All Positive Reactions | | |
| Antigen | Number of Cases | E. histolytica Found by Microscopic Examination, Percentage | Positive Reactions, Percentage | Positive by Both Complement Fixation and Microscopic Examination, Percentage | Probability per 100 Times of Same Combination by Chance | Positive Reactions, Percentage | Positive by Both Complement Fixation and Microscopic Examination, Percentage | Probability per 100 Times of Same Combination by Chance |
| Arnold | | | | | | | | |
| Laboratory C | 37 | 48.6 | 45.9 | 32.4 | 1.6 | 54.1 | 32.4 | 13.4 |
| E. histolytica found | 18 | .... | 66.7 | .... | .... | 66.7 | | |
| E. histolytica not found | 19 | .... | 26.3 | .... | .... | 42.1 | | |
| Craig | | | | | | | | |
| Laboratory B | 110 | 47.3 | 10.9 | 6.4 | 42.4 | 28.2 | 17.7 | 4.5 |
| E. histolytica found | 52 | .... | 13.5 | .... | .... | 36.5 | | |
| E. histolytica not found | 58 | .... | 8.6 | .... | .... | 21.7 | | |
| Craig | | | | | | | | |
| Laboratory A | 75 | 46.7 | 6.7 | 5.3 | 11.0 | 16.0 | 9.3 | 36.8 |
| E. histolytica found | 35 | .... | 11.4 | .... | .... | 20.0 | | |
| E. histolytica not found | 40 | .... | 2.5 | .... | .... | 12.5 | | |
| Sherwood | | | | | | | | |
| Laboratory A | 31 | 51.6 | 16.1 | 9.7 | Exceeds 50.0 | 25.8 | 16.1 | 48.4 |
| E. histolytica found | 16 | .... | 18.8 | .... | .... | 31.3 | | |
| E. histolytica not found | 15 | .... | 13.3 | .... | .... | 20.0 | | |
| Arnold | | | | | | | | |
| Laboratory A | 33 | 24.2 | 0.0 | .... | .... | 0.0 | | |
| E. histolytica found | 9 | .... | 0.0 | .... | .... | 0.0 | | |
| E. histolytica not found | 24 | .... | 0.0 | .... | .... | 0.0 | | |
| All antigens in all laboratories | 150 | 42.7 | 21.3 | 12.7 | 3.6 | 35.3 | 20.0 | 0.9 |
| E. histolytica found | 64 | .... | 29.7 | .... | .... | 46.9 | | |
| E. histolytica not found | 86 | .... | 15.1 | .... | .... | 26.7 | | |

A comparison of the results with the various technics of complement fixation is shown in table 3. As there was no extensive series of multiple serologic reports on the same material, relative evaluations of the probable efficiency of each method were determined by utilizing the statistical approach previously described.

Casual inspection of table 3 shows that the Arnold antigen (laboratory C) gave the highest incidence of positive serologic results in the

cases in which E. histolytica was demonstrated but that it also gave the highest incidence of positive results in the cases in which no amebas were found. When only strong reactions are regarded as positive, the Arnold antigen appears to give highly significant results, which is the more remarkable because of the relatively small number of cases involved. Of all the antigens used, the Arnold antigen, according to the record of positive reactions, seems to be furthest removed from chance association with E. histolytica. When the weakly positive reactions are included as positive, its accuracy in this series becomes less. Apparently this antigen is more sensitive than the others, showing more true positive reactions but also more false positive reactions, especially if partial reactions are considered significant. It should be noted that this antigen was prepared by the originator of the Arnold modification and was used according to the procedures developed by him in his own laboratory. This may have been an advantage not shared by the other laboratories. The fact that the Arnold antigen in laboratory A did not react with any of the serums supports this likelihood.

The Craig antigen seemed to be less sensitive than the Arnold antigen. It was slightly more successful in laboratory B than in laboratory A. Curiously, the inclusion of partially positive reactions with positive reactions in laboratory B increased its relative efficiency, whereas the same manipulation in laboratory A reduced the likelihood of significance. This directs attention to the fact that the same system, but not necessarily the employment of the same materials, in two laboratories may give diverse results, owing perhaps to the use of biologic materials of different strength or age, to apparently unimportant differences in technic or possibly to variations in interpretation, especially of borderline reactions.

The Sherwood antigen, while apparently as sensitive or more so than the Craig antigen, failed to compare favorably from the standpoint of confirming the parasitologic diagnoses.

Summarizing these findings in relation to the chi-square calculations, it is possible to list in order of decreasing significance the results of the serologic reports: (1) the Arnold antigen in laboratory C, partially positive reactions being excluded; (2) the Craig antigen in laboratory B, partially positive reactions being included; (3) the Craig antigen in laboratory A, partially positive reactions being excluded, and (4) the Sherwood antigen in laboratory A, partially positive reactions being included. It is possible, as has already been shown (table 2), that a positive reaction was associated with known amebiasis more frequently in cases of "amebic dysentery" and "varied abdominal symptoms" than in the cases of other dysenteries and diarrheas and that some of the apparent differences in the accuracy of the various sero-

logic systems may have been due to an unequal representation of the clinical types tested in each system. Nothing more than fortuitous factors influenced the distribution of the serums to the laboratories, as is indicated by the percentage of specimens examined by each laboratory from patients in whom E. histolytica was found (table 3) in comparison with the percentage of cases in the entire group in which E. histolytica was demonstrated. The specimens examined in laboratory A with the Arnold antigen constitute a minor exception; but as no positive reaction was reported, no conclusions are drawn regarding it.

## COMMENT

At the outset of this study it was recognized that our experience with complement fixation in the diagnosis of amebiasis could hardly be expected to give as auspicious results as those obtained in the development and evolution of the technic. We could only hope that our experience would be fairly representative of that of the clinician who, having exhausted other facilities for the solution of differential diagnosis in some of his more perplexing cases of abdominal disorders, undertakes to obtain additional diagnostic information by sending serum to a laboratory for a report on the complement fixation with regard to amebiasis.

The disparity between the results reported and those of the original investigators was undoubtedly conditioned by a number of factors. Our clinical material was derived from hospital and private patients and in many instances was not under our complete control. While our medical colleagues were always cooperative, they were frequently satisfied with a less extensive study of stools than we desired. Some patients were available for only brief periods for a diagnostic survey. There were no opportunities for checking our results in these cases. These are difficulties inherent in clinical practice. Our serologic reports came from laboratories where the work was treated as part of the routine. It did not, therefore, in all probability, receive the special attention that it might have been accorded had it been a special research project. We have no way of estimating the original potency of the antigens used, their age or the care with which they were employed or of finding out whether special controls, such as serums known to react strongly with the antigen, were always used. However, as these laboratories make a specialty of serologic diagnosis, we can assume that their materials were used to the best advantage. The serum was in all cases obtained before therapy was instituted.

The parasitologic diagnoses were made by specialized workers in this field who had no other professional concern.

Thus our results must be interpreted as relative rather than absolute evaluations of complement fixation in amebiasis. For example, in 66.7 per cent of our cases of amebic dysentery there were positive serologic reactions, whereas Sherwood and Heathman [3] reported positive complement fixation in "nearly 100 per cent," Tsuchiya [5] in 83.3 per cent and Weiss and Arnold [4] in 75 per cent of their respective cases. Craig [11] noted 3 instances of amebic dysentery in which the serologic reactions were negative. Under the circumstances it is perhaps surprising that we obtained as favorable and reasonable correlations as we did. We consider that we have subjected the technic to a most rigorous and trying test, but one which it must face if it is to be employed diagnostically in clinical practice.

To the clinician the most practical utility of the complement fixation test for amebiasis would be in assisting him to determine the etiologic factor in the dysentery-diarrhea group of diseases, especially when no other specific basis for the manifestations can be demonstrated. When all the cases studied are considered, our data reveal a statistically valid relation between the presence of complement-fixing bodies and the protozoologic evidence of amebiasis, confirming in general the specificity of the technic developed by Craig and others. However, from a practical diagnostic standpoint the test has the disadvantage of giving too many falsely positive as well as falsely negative responses, thus tending materially to vitiate its diagnostic import in an individual case. The reaction has been found to be least reliable in the clinical groups in which it might be most useful. Thus, when Kiefer [10] submitted 16 serums to Craig for complement fixation for amebiasis, positive reactions were reported for 12 (75 per cent), though E. histolytica was not found. Craig [11] mentioned obtaining positive reactions in 11 cases of chronic ulcerative colitis in which amebas were not found, though he expressed the opinion that inadequate studies of the stools were made in these cases. Tsuchiya [5] reported that in 4 (44.4 per cent) of 9 cases of nonamebic ulcerative colitis a positive reaction was obtained. Our own data (table 2) indicate that in about 30 per cent of the cases of ulcerative colitis and in a similar proportion of the cases of chronic diarrhea in which E. histolytica was not demonstrated a positive reaction was obtained. Thus in a considerable number of cases of acute and subacute inflammatory processes of the large bowel in which E. histolytica was not demonstrated there was a positive reaction with amebic antigen. The explanation previously given for this discrepancy was that the stools of these patients were not studied over a sufficiently long period to disclose the parasite or that a secondary infection was superimposed on an original amebic lesion. Both Kiefer and Craig have supported this opinion by citing instances of apparent specific responses to amebicidal therapy in cases in which complement

fixation tests showed a positive reaction. Information concerning these responses is vague and inconclusive, but it is evident that the responses are not uniform and that in many instances they are incomplete. They are hardly comparable to the dramatic abrupt recoveries usually manifested when specific antiamebic drugs are administered in cases of amebic colitis. It is questionable whether the observed rate of recovery exceeded that in cases of ulcerative colitis in which amebicidal treatment is not given but in which rest and special dietary and adjunctive symptomatic measures are employed. Chronic ulcerative colitis is a disease characterized by spontaneous intermissions or remissions and recurrences. After amebicidal therapy, which included the use of emetine hydrochloride, arsenicals and oxyquinoline derivatives, we have observed both amelioration and unimprovement in cases of ulcerative colitis in which positive and negative reactions to complement fixation tests were obtained.

Despite these observations, complement fixation in the diagnosis of amebiasis holds much promise, as evidenced by the observed concurrence of demonstrated amebiasis and positive fixation. However, improvements in antigen and in technic—both of which are likely to come—are essential before satisfactory use of the test can be made clinically. At present, for accurate diagnosis the clinician must still rely on multiple examinations of dejecta by competent observers. Indeed, Craig has stated that when adequate examinations of stools are made the test is unnecessary. The report of positive complement fixation can only direct the attention of the physician to the probability of amebiasis.

## SUMMARY AND CONCLUSIONS

Serums from 150 persons studied clinically and parasitologically were submitted for complement fixation tests to one or more of three different laboratories in which one or more of three different types of specific antigens were employed.

When the patients were assembled into roughly homogeneous clinical groups, the incidence of positive results of complement fixation was regularly higher for those in whom E. histolytica was found microscopically than for those in whom the organism was not found. For the 150 patients considered as a whole the difference was statistically significant. For the 136 patients with symptoms it was even more highly significant, but in none of the clinical subdivisions was it statistically valid. Thus, our results confirm in general the specificity of the technic developed by Craig and others. However, from a practical diagnostic standpoint the too numerous falsely positive as well as falsely negative responses obtained under the conditions of our observation show that the test is unreliable in the individual case.

This reaction is not helpful in the cases in which it might be most useful to the clinician, in that the least significant coincidences occur in the cases of so-called indeterminate diarrhea and dysentery. In cases of chronic ulcerative colitis and chronic or intermittent diarrhea many positive reactions are obtained that are unassociated with demonstrable amebiasis.

While the general mass of serologic reports from different laboratories and with different antigens showed a fair degree of agreement, conspicuous disagreement occurred in some instances.

Of the various antigens and serologic systems employed, the most successful results, based on parasitologic diagnoses, were obtained with the Arnold antigen in Arnold's laboratory.

Statistical analysis of the partially positive reactions indicated the desirability of including them as positive reactions when obtained with relatively weak antigens and of excluding them from consideration when obtained with very sensitive antigens.

We are of the opinion that complement fixation is at present a diagnostic aid of adjunctive rather than of primary value. Its more successful application in clinical practice awaits further refinement. It should not be relied on as a diagnostic criterion unsupported by parasitologic evidence of infection. Notwithstanding the many defects of microscopic fecal diagnosis of amebiasis, this method is today more dependable than complement fixation.

NOTE.—Since this paper was accepted for publication, two reports have appeared to which reference must be made for completeness: Meleney and Frye [12] have pointed out that the test is still in its developmental stage; that many infections with E. histolytica were associated with positive complement fixation reactions; that a significant number of patients harboring "E. histolytica in the intestine gave negative complement fixation reactions." They concluded that a "positive complement fixation reaction in man is presumptive evidence of the presence of ameba in the tissues, and that most infected persons giving a negative reaction (except those in the early stage of the infection) harbor the parasite only in the lumen of the intestine without tissue invasion." They dismiss their positive complement fixation reactions in ulcerative colitis when E. histolytica was not found as probably amebic in origin because of marked clinical improvement on administration of carbarsone. This phase of the question has already been discussed elsewhere in this paper.

12. Meleney, Henry E., and Frye, William W.: Practical Value and Significance of the Complement Fixation Reaction in Amebiasis, Am. J. Pub. Health **27**:505-510, 1937.

Weiss and Arnold [13] have reported important changes in their modification of the complement fixation test for amebiasis resulting in a high correlation of positive reactions with the finding of E. histolytica and in negligibly few false positive responses in controls. Unfortunately, there are no specific data as to the reactions of serums from those with nonamebic intestinal involvement to this altered procedure. Its use after the manner of the several procedures employed in this study seems essential before the latest Weiss-Arnold modification can be adequately evaluated in clinical practice.

13. Weiss, Emil, and Arnold, Lloyd: A Complement Fixation Test for Amebiasis with an Increased Antibody Content, Am. J. Digest. Dis. & Nutrition **4**:282-287, 1937.

# HYPERINSULINISM AND CEREBRAL CHANGES

## REPORT OF A CASE DUE TO AN ISLET CELL ADENOMA OF THE PANCREAS

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In insulin hypoglycemia, or hyperinsulinism, whether spontaneous or induced, the manner in which the nervous system is affected is of primary interest. This has been investigated (1) in "insulin shock" of patients suffering from diabetes, (2) in spontaneous hypoglycemia due to neoplasm or to hypertrophy or functional oversecretion of the islands of Langerhans and (3) under experimental conditions. We wish to report a case of spontaneous hypoglycemia due to an adenoma of the islands of Langerhans. On the basis of our study of this case and a survey of the literature, an attempt will be made to correlate the clinical, laboratory and anatomic data on this disorder from the pathogenic standpoint.

### REPORT OF CASE

*History.*—A. P., a married woman aged 30, was admitted to the Ypsilanti State Hospital on March 16, 1936. The family history and the patient's past history were essentially unimportant. She had been in good health until 1930, when she began to have "fainting spells." These frequently occurred in the morning, were usually followed by a "craving for sweets" and were relieved by food. There was a gradual change to convulsive attacks, which were initiated by excessive perspiration and flushed facies. She consumed large amounts of sweets and gained rapidly in weight. In the intervals between attacks she was normal until November 1934, when the convulsions became more frequent and a definite mental change occurred. She became irritable, resistive and impulsive. This was followed by gradual emotional and mental decline. In July 1935 and again in February 1936 the patient was admitted to a private hospital in a semicomatose state. She was out of touch with her surroundings and restless, had convulsions and was incontinent. On her second admission to the hospital the fasting level for blood sugar was found to be 60 mg. per hundred cubic centimeters, with 37.5 mg. of sugar per hundred cubic centimeters of spinal fluid. No definite diagnosis was made, and the patient was transferred to the Ypsilanti State Hospital.

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From the Laboratory of the Neuropsychiatric Institute, University of Michigan, Dr. Raymond W. Waggoner, director, and the Ypsilanti State Hospital, Dr. George F. Inch, superintendent.

*Status on Admission to the Hospital.*—The patient was confused, restless and negativistic. She uttered peculiar cries but remained otherwise mute. There were marked generalized rigidity, drooling, excessive perspiration and incontinence of urine and feces. Otherwise the neurologic and general physical examinations revealed no abnormality.

*Laboratory Data.*—The urine contained 1+ albumin and many white blood cells but no sugar. Examination of the blood disclosed 5,200,000 red cells and 13,150 white cells per cubic millimeter, with 81 per cent neutrophils, 12 per cent lymphocytes and 7 per cent monocytes; the hemoglobin value was 90 per cent (Sahli). The Kahn tests of the blood and spinal fluid gave negative results. Simultaneous tests of the blood and spinal fluid during fasting revealed 35 mg. of sugar per hundred cubic centimeters of blood and 17.5 mg. of sugar per hundred cubic centimeters of spinal fluid. Chemical examination of the blood showed: cholesterol, 174.4 mg.; calcium, 10.6 mg., and phosphorus, 5 mg., per hundred cubic centimeters.

In table 1 (condensed from table 2) are shown the results of sixteen determinations of the initial fasting level of the blood sugar made on different days. The high incidence of marked hypoglycemic levels (ten of sixteen readings) is obvious.

TABLE 1.—*Fasting Levels of Blood Sugar*

| Sugar, Mg. per 100 Cc. | Number of Determinations | Range of Oral Temperature, Degrees F. |
|---|---|---|
| 30-40 | 6 | 97.8-98.8 |
| 40-50 | 4 | 98.0-99.0 |
| 50-60 | 3 | 98.6-99.0 |
| 60-70 | 1 | 98.6 |
| 94 | 1 | 99.4 |
| 130 | 1 | 100.0 |

The normal and high readings were associated with fever. The blood sugar level after a twenty-four hour fast was not lower than that after the usual fasting period. It was noted also that active resistiveness during venipuncture tended to raise the fasting level.

The results of the various dextrose tolerance tests are given in table 2. With a normal diet, other conditions (dextrose dosage, temperature and nonadministration of sedatives) being constant, the type of curve obtained was consistently characterized by a rise in the blood sugar level, which was maintained through the two hour period, and by a delay in fall to hypoglycemic levels (the "plateau type" of curve). In the accompanying chart (fig. 1), two such curves (*a* and *b*) are illustrated and represent the variations which occur in typical curves even under standard conditions. Also included in this chart is a typically "diabetic curve" (*c*) which was associated with a change in the factor of temperature (100 F.), even though the other conditions remained the same. With the high carbohydrate diet, the maximum rise was not quite so pronounced, but the subsequent fall was not lower than that shown with the previous normal diet. Nevertheless, it was noted that the convulsions had their onset during the period of high intake of carbohydrate. The low carbohydrate diet could not be carried out for a sufficiently prolonged period for adequate study.

Two types of hepatic function tests were made: 1. In order to test the adequacy of the glycogen stores, the patient was given on three occasions injec-

TABLE 2.—*Fasting Level of Blood Sugars and Dextrose Tolerance Tests* *

| Date | Fasting Level | Hours | | | | | | | | | | Temperature (Oral) Range, Degrees F. | Diet |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ½ | 1 | 1½ | 2 | 2½ | 3 | 3½ | 4 | 4½ | 5 | | |
| 3/24 | 35.0 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | .... | .... | 98 | Normal |
| 3/26 | 31.0 | 190.0 | 250.0 | 215 | ..... | 190 | ... | 179.0 | .... | .... | .... | .... | 98.6-98.8 | Normal |
| 3/27 | 37.9 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | .... | .... | 98 | Normal |
| 3/28 | 57.0 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | .... | .... | 99 | Normal |
| 3/29 | 46-37 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | .... | .... | 98-98.4 | Normal |
| 4/ 4 | 68.3 | 181.6 | 181.6 | ... | 178.6 | 136 | 97.0 | 71.4 | 48.6 | 52.5 | 55.1 | 98.6-99 | Normal |
| 4/ 9 | 58.6-42 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | .... | .... | 98.6-98.8 | Normal |
| 4/14 | 39.2 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | 43.0 | .... | 98.2-99 | Normal |
| 4/17 | 94.0 | ..... | ..... | ... | ..... | ... | 208 | ..... | .... | 102.0 | .... | .... | 99.4-101 | Normal |
| 4/22 | 41.0 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | 43.0 | .... | 98.6-98.8 | Normal |
| 4/25 | 44.0 | ..... | ..... | 209 | ..... | ... | 112.1 | .... | .... | 48.0 | .... | 98-97.8 | High carbohydrate |
| 5/28 | 34.0 | ..... | ..... | ... | ..... | ... | ..... | .... | .... | .... | .... | ..... | High carbohydrate |
| 5/29 | 51.0 | ..... | ..... | ... | 153 | ..... | 132 | ..... | 57.0 | .... | .... | 35.6 | 97.8-98.2 | High carbohydrate |
| 6/16 | 36.3 | ..... | 121.0 | ... | 119.5 | ... | 44.0 | .... | 30.0 | .... | 55.0 | 98-98.8 | Normal |
| 7/ 3 | 130.0 | ..... | 330.0 | ... | 300.0 | ... | 230.0 | .... | 155.0 | .... | .... | 100 | Normal |
| 7/ 6 | 48.0 | ..... | 158.0 | ... | 133.0 | ... | 84.0 | .... | 44.0 | .... | 48.0 | 99-99.6 | Low carbohydrate |

* The dose of dextrose given was 1 Gm. per kilogram of calculated average body weight; the customary 1.75 Gm. per kilogram given at first (on March 26) produced vomiting. All the determinations of the blood sugar were carried out on venous blood after the method of Folin and Wu, and the results are given in milligrams per hundred cubic centimeters.

tions of epinephrine hydrochloride; the results are recorded in table 3. These demonstrate that there was apparently an adequate amount of glycogen present for mobilization. It was most strikingly shown during the test made on April 9. On this date, although an attempt was made to deplete the glycogen store of the liver by twenty-four hours of starvation, the response was in every way comparable to the responses to the other tests. 2. The bromsulphalein test showed a retention of less than 15 per cent on two occasions. The bilirubin content of the blood was 0.2 mg. per hundred cubic centimeters. The icterus index was 9.

*Comment.*—An islet cell neoplasm of the pancreas was suspected because of the high ("plateau") type of sugar tolerance curve obtained, the consistently severe hypoglycemia and the absence of adrenal, thyroid or pituitary dysfunction. However, disease of the liver could not definitely be ruled out, in spite of the negative

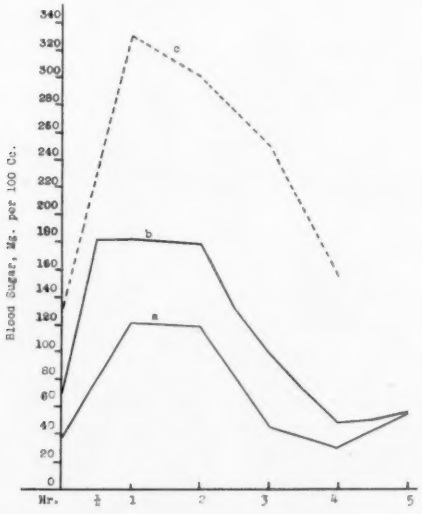


Fig. 1.—Dextrose tolerance curves.

results of the hepatic function tests. An exploratory operation on the pancreas did not appear justified, since there was no change in the clinical picture when the blood sugar was maintained at an approximately normal level for long periods by dietary measures. Moreover, the patient was obviously a poor "operative risk."

*Clinical Course.*—Throughout her stay in the hospital the patient remained semistuporous, mute, negativistic, restless and incontinent of urine and feces. It was noted that at times she blinked her eyes or closed one eye when attempting to look at any one, suggesting the presence of diplopia. Arthritis deformans, with contractures of the fingers, gradually developed. On June 12 the patient suddenly became pale, drowsy and restless, her eyes closed and her lips drooped. This seizure lasted for twenty minutes. Two days later she had an attack lasting for three minutes, which began with a peculiar cry and was followed by spasmodic jerking of the trunk and arms, frothing at the mouth, a staring expression, dilatation of

the pupils, perspiration and stertorous breathing. On June 18 there was another attack, with cyanosis, drooling, tonic and clonic spasms of the whole body followed by a staring expression, loud snoring and continuous swallowing movements. A similar attack occurred the following day. The next seizure occurred on July 2, but the convulsions changed from a generalized to a jacksonian type. This was characterized by spasmodic twitchings, which spread along the right upper extremity and occasionally involved the right side of the face and right lower extremity, the eyes deviating variously to the right and to the left. This type of seizure persisted without interruption until two weeks before death. At the same time cystitis developed and the temperature rose to 102 F. per rectum, remaining elevated until death occurred. On July 31 the convulsions suddenly ceased, and the patient gradually sank into a deep coma. On August 13 the temperature rose to 106.5 F., and signs of bronchopneumonia developed. Blood sugar determinations were in the neighborhood of 200 mg. per hundred cubic centimeters just before the patient expired.

*Necropsy.*—Ten minutes after death, hepatic tissue was removed and macerated in 20 per cent solution of potassium hydroxide for a determination of the glycogen content. The average reading obtained was 0.5 per cent hepatic glycogen,

TABLE 3.—*Response During Fasting of Blood Sugar Content to Epinephrine* *

| Date | Blood Sugar, Mg. per 100 Cc. | | | Oral Temperature, Degrees F. |
|---|---|---|---|---|
| | Initial Value | ½ Hour After Injection of Epinephrine | 1 Hour After Injection of Epinephrine | |
| 3/28/36 | 57 | 115.3 | 181.0 | 99 |
| 3/29/36 | 46-37 | 111.0 | 169.9 | 98-98.4 |
| 4/ 9/36 | 58.6-42 | 92.0 | 170.0 | 98.6-98.8 |

* Injections of 1 cc. of 1:1,000 solution of epinephrine hydrochloride were given during fasting.

determined as dextrose-reducing substance.[1] Within two and one-half hours the complete necropsy was performed. The body appeared well developed and fairly well nourished. There were contractures of both hands. The pancreas was of normal size and had an essentially normal external appearance. However, section revealed a solitary yellowish spherical encapsulated tumor, measuring 1.1 by 0.9 by 1 cm., and embedded within the head of the pancreas near its junction with the body. The liver had a fatty, nutmeg appearance. A tumor the size of a small walnut was seen in the thyroid gland; multiple small cysts surrounded the left ovary. There were, in addition, bronchitis, bronchopneumonia and generalized passive congestion.

The microscopic examination of the tumor in the pancreas revealed an encapsulated adenoma consisting of tissue closely resembling normal structure of the islands of Langerhans (fig. 2*A*). The epithelial tissue was arranged either in long convoluted cell cords or in the form of tubules about capillaries (fig. 2*B*). The cells were cuboid or cylindric, with large vesicular darkly staining nuclei. The epithelial cells were in intimate contact with the capillaries, and there was no membrana propria. A delicate connective tissue stroma traversed the tumor, and a well defined fibrous capsule surrounded it. Otherwise, the pancreas disclosed a moderate increase in the number of islands of Langerhans, which were, how-

1. This test was performed by Dr. J. W. Conn, of the Department of Internal Medicine, the University of Michigan.

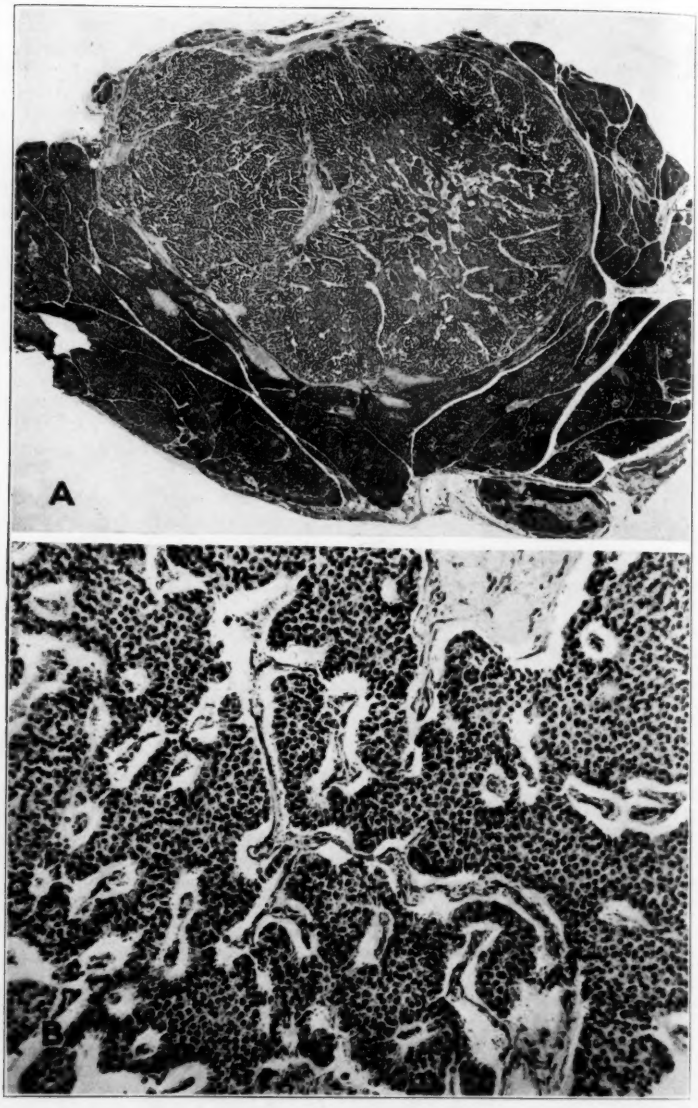


Fig. 2.—*A*, encapsulated islet cell adenoma, with moderate hyperplasia of the islands of Langerhans in the surrounding pancreas. Hematoxylin and eosin stain; photomicrograph; Zeiss planar, 50 mm. *B*, higher magnification of *A*, showing the architecture of the tumor. The tissue is composed of a syncytium of cords and tubules of epithelial cells arranged about capillaries. Hematoxylin and eosin stain; photomicrograph; Zeiss objective, 16 mm.; projection ocular, no. 2.

ever, not hypertrophied; the acinous tissue, the blood vessels and the connective tissue stroma were normal. In the liver there were scattered focal accumulations of lipoids in the form of fatty infiltration and degeneration. The latter occurred chiefly in congested and atrophic lobules about the central veins; there was no increase in the amount of connective tissue. There was lipoidosis of the cortex of the adrenal glands.[2] The tumor in the thyroid gland was histologically a colloid cystic adenoma. In the hypophysis there was diffuse eosinophilic hyperplasia, and a small basophilic adenoma was seen in the anterior lobe. There were, in addition, chronic catarrhal endocervicitis, old hyaline corpora fibrosa in the ovaries, purulent bronchitis and early bronchopneumonia, moderate brown atrophy of the myocardium, early phlegmon of the breast and passive congestion of the spleen, liver, kidneys, lungs and gastro-intestinal tract.

The brain weighed 1,125 Gm. The leptomeninges were thin and moderately congested; the basal vessels were delicate. The convolutions were well developed. In coronal sections the cortex was for the most part well demarcated from the white matter and moderately hyperemic, but in the left hemisphere there were scattered areas in which the gray matter was narrow and appeared spongy. The ventricles were of normal width, and the ependyma was smooth. The basal ganglions, brain stem, cerebellum and cervical portion of the spinal cord were grossly normal. The pineal gland was cystic.

In the pia-arachnoid there was slight fibroblastic thickening. The meningeal vessels were moderately distended and congested but otherwise normal.

In the cerebral cortex of both hemispheres there was distinct universal parenchymatous degeneration, more pronounced in the left hemisphere and varying in intensity in different regions. The most striking feature of the degenerative process was its laminar character, which was noted throughout the gray matter. Layers 3 and 5 were most commonly and severely involved. In some areas the degeneration extended also into layers 2 and 6, whereas the fourth layer was usually well preserved. In the first layer there was considerable gliosis. On the whole, the laminar degeneration could be subdivided according to the degree and sequence of involvement into the following types: (1) paling (*Erbleichung*) of laminae 3 and 5, with neither appreciable loss of nerve cells nor glial reaction (fig. 3*A*); (2) moderate degeneration of laminae 3 and 5, with loss of neurons and beginning glial reaction, chiefly microglial; (3) severe degeneration of laminae 3 and 5, accompanied with pronounced gliosis and varying involvement of laminae 2 and 6 (fig. 3*B*), and (4) severe destruction of all layers except the fourth, associated with cortical atrophy and status spongiosus.

Examination of the left hemisphere revealed that the cortex of the frontal lobe was moderately involved (type 1), severe laminar degeneration being restricted to the gyrus cinguli. Starting with the precentral region and extending posteriorly throughout the entire hemisphere, the degeneration was severe (types 3 and 4) in both the isocortex and the allocortex. In the latter the nucleus amygdalae and the uncus were completely degenerated. In the cornu ammonis the involvement was selective, the fascia dentata being well preserved, but the end-plate and the resistant part were completely degenerated (fig. 4). Sommer's sector was relatively well preserved, but there was increasing severity of the degeneration in the subiculum and presubiculum, which merged with that of the temporal lobe. In the right hemisphere, in contrast to the picture on the left side, there was uniformly mild

2. The organs of internal secretion and the reproductive organs were examined by Prof. Carl V. Weller, of the Department of Pathology, the University of Michigan.

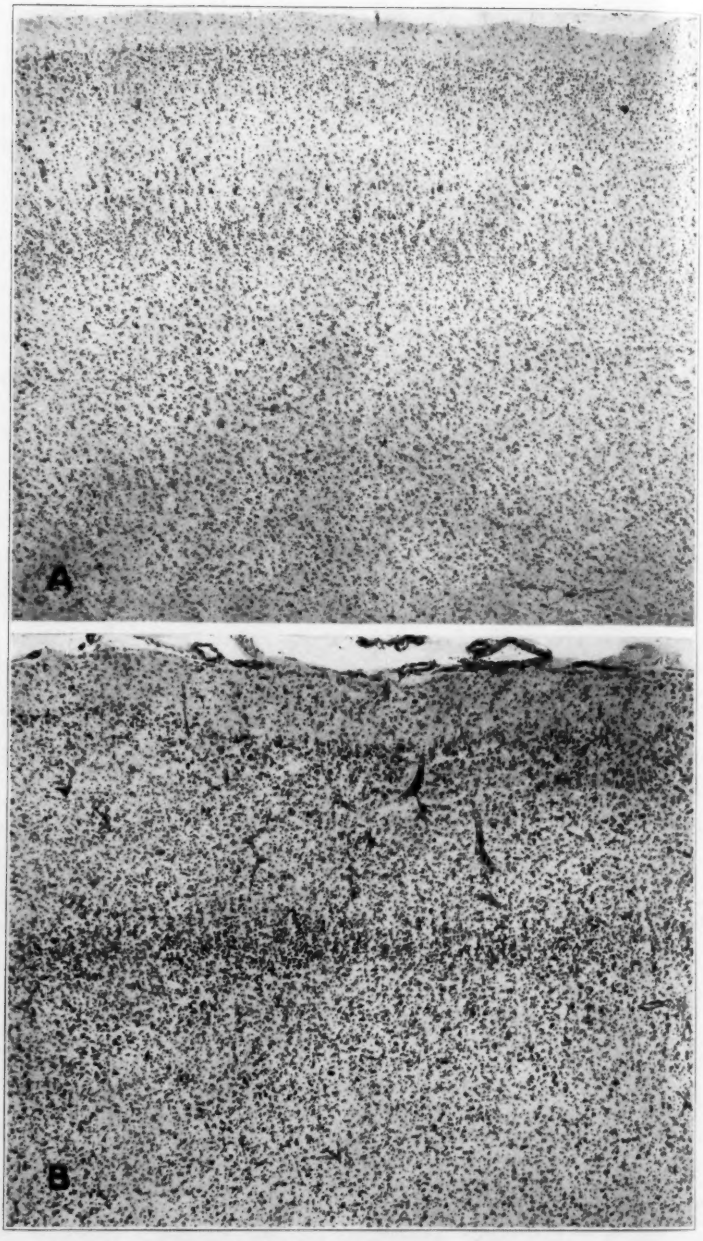


Fig. 3.—*A*, cortex of the right parietal region, showing laminar paling (*Erbleichung*) of the parenchyma in layers 3 and 5. Nissl stain; photomicrograph; Zeiss planar, 20 mm. *B*, cortex of the left parietal region, showing laminar degeneration and gliosis involving layers 3 and 5 and encroaching on layers 2 and 6. Nissl stain; photomicrograph; Zeiss planar, 20 mm.

involvement of type 1 in the entire gray matter, with the exception of the gyrus cinguli, where the degeneration was similar to that of the left side.

The changes in the neurons were predominantly those of "Nissl's acute swelling." The cells and their dendrites were swollen, there was chromatolysis of the tigroid substance and the cytoplasm was homogeneous and pale. The nuclei were swollen, but their structure remained otherwise intact. The neurofibrils were disintegrated in the center but were preserved at the periphery of the cell and in the dendrites. The cells contained occasional lipoid droplets. In severely degenerated areas the neurons were either reduced to shadows or completely destroyed. "Nissl's severe change," incrustation and inflated elements were rare. The axis-cylinders were reduced in number, frequently fragmented and

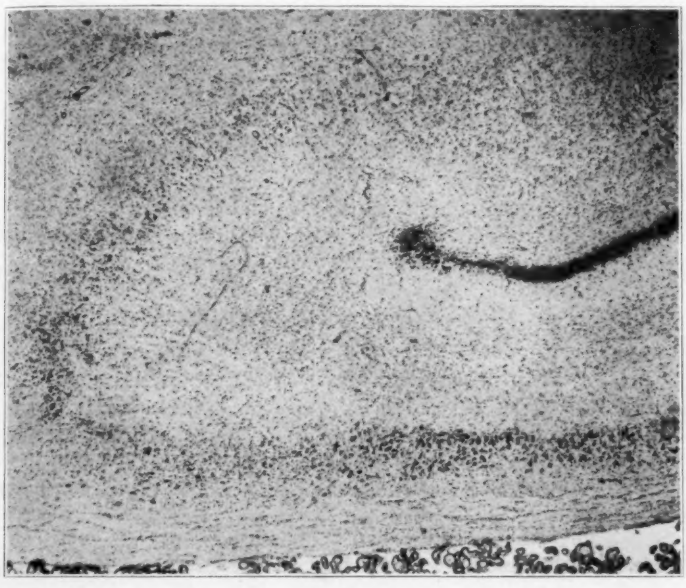

Fig. 4.—Cornu ammonis of the left hemisphere. Note the selective involvement of the resistant part and end-plate and the preservation of Sommer's sector. Nissl stain; photomicrograph; Zeiss planar, 20 mm.

swollen. Weigert preparations showed demyelinization and reduction of the tangential and radial fibers of the cortex. In less involved regions the microglia was greatly proliferated and contained considerable lipoid deposits, whereas in severely degenerated areas the astrocytes predominated, forming a dense glial network. There was also an increase in marginal, subependymal and perivascular gliosis. There were regressive changes in the oligodendroglia; neuronophagia was common in degenerated areas. The blood vessels contained a few droplets of fat in the adventitia but were otherwise essentially normal. There was no iron.

The white matter was essentially normal, with only slight rarefaction in the myelin sheaths and moderate increase in the number of glial fibers. The choroid plexus and the ependyma were normal.

Examination of the basal ganglions showed distinct changes in the caudate nucleus and putamen of each side, more pronounced on the left, disclosing diffuse degeneration of the small ganglion cells, whereas the large ganglion cells were well preserved; there was moderate proliferation of the glia. There were no significant changes in the pallidum. The thalamus was severely involved bilaterally, especially in the left pulvinar, in which the neurons were greatly reduced in number and the microglia and macroglia were proliferated.

In the corpus Luysi, hypothalamus, brain stem, cerebellum and cervical portion of the spinal cord there was only diffuse swelling of the neurons.

## REVIEW OF THE LITERATURE

*A. Clinical Observations.*—From a clinical standpoint the symptoms of hyperinsulinism are variable and have been so well outlined by a number of authors that they will be only briefly referred to here. According to Wilder,[3] the symptoms may be classified into (1) disorders of the vegetative nervous system (perspiration, salivation and changes in heart rate), (2) organic neurologic symptoms (convulsions, periods of coma and focal signs) and (3) psychopathologic manifestations (psychoneuroses and psychotic states). Bowen and Beck[4] concluded that the initial symptoms are vegetative phenomena caused by "epinephrine discharge" (Cannon) and followed by manifestations referable to the central nervous system.

*B. Laboratory Observations.*—The various laboratory data on "spontaneous" hyperinsulinism reported in the literature will be considered according to four general etiologic groups: (1) neoplasms of the islands of Langerhans, (2) hypertrophy or hyperplasia of the islands of Langerhans, (3) hyperinsulinism ameliorated by partial resection of the normal pancreas and (4) functional hyperinsulinism generally benefited by dietary therapy. For the first two groups the etiology is established, in the third it is highly suggestive but in the last group it is problematic. In accordance with this classification, table 4 (page 595) includes a grouping of the dextrose tolerance curves in ninety-nine cases reported in the literature, as well as the type of response to epinephrine when recorded.[5]

The dextrose tolerance curves reported are here arbitrarily subdivided into two distinct types: (*a*) the high, sometimes "plateau" or even "diabetic" type of curve, which is characterized by an initial rise,

3. Wilder, J.: Zur Neurologie und Psychiatrie der hypoglykämischen Zustände, Med. Klin. **26**:616 (April 25) 1930.

4. Bowen, B. D., and Beck, G.: Insulin Hypoglycemia, Ann. Int. Med. **6**: 1412 (May) 1933.

5. This review was restricted to articles in English. The cases of hypoglycemia reported by P. J. Cammidge (Hypoglycemia, Lancet **2**:1277 [Dec. 20] 1924; Chronic Hypoglycemia, Brit. M. J. **1**:818 [May 3] 1930) are not included, because that author said he did not regard them as due to hyperinsulinism.

usually abrupt, and is invariably maintained above the average normal fasting level for blood sugar through the two hour period before the eventual return to hypoglycemia sets in (delayed hypoglycemic response); and (*b*) the low, sometimes flat type of curve, which occasionally shows a definite rise within the first hour but is always well below the average normal fasting level for blood sugar by the second hour, when it is often definitely hypoglycemic (accelerated hypoglycemic response). The two unclassified tests included in table 4 are not characteristic of either *a* or *b*, in that they show a delayed rise occurring between one and one-half and two hours, which is often considered as signifying a delay in the absorption of the dextrose. Such variable factors as previous diet, temperature, dosage of dextrose and medication, which alter the dextrose tolerance test, are frequently not mentioned in the literature. Therefore, one must assume in such a classification that the patient with hyperinsulinism had at least an adequate amount of carbohydrate in his diet, that he did not have fever or did not need sedative medication and that a standardized dose of dextrose was given for the test. The various results of the dextrose tolerance test will be discussed further presently.

In general, the reported average fasting level for blood sugar is low, particularly for the groups of patients with neoplasm and hypertrophy of the islet cells, but occasionally it is relatively normal.

The response to epinephrine is considered to be adequate when within an hour after the injection there is a rise of the blood sugar level from hypoglycemic to normal or higher levels, usually with the relief of symptoms. Occasionally, in the absence of determinations of the blood sugar level, the response is thought adequate if the symptoms are quickly and adequately relieved.

Other hepatic function tests in these cases, such as the injection of bromsulphalein or phenoltetrachlorphthalein, the van den Bergh reaction and the determination of the bilirubin content of the blood, gave normal results when reported [6] except in two cases (Rynearson,[6q] and Judd,

6. (*a*) Wilder, R. M.; Allen, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927. (*b*) Howland, G.; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism: Convulsions and Coma Due to Islet-Cell Tumor of the Pancreas with Operation and Cure, ibid. **93**:674 (Aug. 31) 1929. (*c*) Carr, A. D.; Parker, R.; Grove, E.; Fisher, H. O., and Larrimore, J. W.: Hyperinsulinism from Beta Cell Adenoma of the Pancreas; Operation and Cure, ibid. **96**:1363 (April 25) 1931. (*d*) Womack, N. A.; Gnagi, W. B., and Graham, E. A.: Adenoma of the Islands of Langerhans with Hypoglycemia: Successful Operative Removal, ibid. **97**:831 (Sept. 19) 1931. (*e*) Bast, T. H.; Schmidt, E. R., and Severinghaus, E. L.: Pancreatic Tumor with Hypoglycemia: Status Epilepticus, Acta chir. Scandinav. **71**:82, 1932. (*f*) Derick, C. L.;

*(Footnote continued on next page)*

Faust and Dixon [61]) in which hepatitis was present at biopsy. Adequate amounts of glycogen in the liver were reported by Wilder and his associates,[6a] McClenahan and Norris,[7] and Cragg, Power and Lindem.[6v] Terbrüggen [8] and Rienhoff and Lewis,[6k] on the other hand, observed no glycogen in the liver on histologic examination.

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Newton, F. C.; Schutz, R. Z.; Bowie, M. H., and Pokorny, N. A.: Spontaneous Hyperinsulinism, New England J. Med. **208**:293 (Feb. 9) 1933. (*g*) Graham, E. A., and Womack, N. A.: The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and to Other Conditions, Surg., Gynec. & Obst. **56**:728 (April) 1933. (*h*) Wolf, A.; Hare, C. C., and Riggs, H. W.: Neurological Manifestations in Two Patients with Spontaneous Hypoglycemia with Necropsy Report of Case of Pancreatic Island Adenoma, Bull. Neurol. Inst. New York **3**:232 (June) 1933. (*i*) Ziskind, E.: Hyperinsulinism: Report of Case of Spontaneous Hypoglycemia with Studies in Dextrose Tolerance, Arch. Int. Med. **52**:76 (July) 1933; personal communication to the authors. (*j*) Ross, L. I., and Tomasch, J. M.: Hyperinsulinemia, Secondary to an Adenoma of the Pancreas: Report of a Case with Operative Cure, Arch. Surg. **28**:223 (Feb.) 1934. (*k*) Rienhoff, W. F., Jr., and Lewis, Dean: Surgical Affections of the Pancreas Met with in the Johns Hopkins Hospital from 1889 to 1932, Including a Report of a Case of an Adenoma of the Islands of Langerhans, and a Case of Pancreato-Lithiasis, Bull. Johns Hopkins Hosp. **54**:386 (June) 1934. (*l*) Judd, E. S.; Faust, L. S., and Dixon, R. K.: Carcinoma of the Islands of Langerhans with Metastasis to the Liver Producing Hyperinsulinism, West. J. Surg. **42**:555 (Oct.) 1934. (*m*) Whipple, A. O., and Frantz, V. K.: Adenoma of Islet-Cells with Hyperinsulinism, Ann. Surg. **101**:1299 (June) 1935. (*n*) Feiner, L.; Soltz, S. E., and Haun, P.: The Syndrome of Adenoma of the Pancreas, Bull. Neurol. Inst. New York **4**:310 (Oct.) 1935. (*o*) Liu, S. H.; Loucks, H. H.; Chou, S. K., and Chen, K. C.: Adenoma of Pancreatic Islet Cells with Hypolycemia and Hyperinsulinism: Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, J. Clin. Investigation **15**:249 (May) 1936. (*p*) Kepler, E. J., and Walters, W.: Chronic Hypoglycemia Caused by Hyperinsulinism: Cure Effected by Removal of Adenoma of Pancreas, Proc. Staff Meet., Mayo Clin. **11**:454 (July 15) 1936. (*q*) Rynearson, E. H.: Adenoma of the Islands of Langerhans: Two Cases, ibid. **11**:451 (July 15) 1936. (*r*) Long, C. F.; Sheplin, L., and Fishbach, D. B.: Spontaneous Hyperinsulinism Due to Pancreatic Adenoma in a Patient with Carcinoma of the Sigmoid: A Catastrophic Conjunction, Am. J. Digest. Dis. & Nutrition **3**:488 (Sept.) 1936. (*s*) Aitken, L. F.: Diagnosis and Treatment of Hyperinsulinism, M. Clin. North America **20**:393 (Sept.) 1936. (*t*) McCaughan, J. M., and Broun, G. O.: The Value of Partial Pancreatectomy in Convulsive States Associated with Hypoglycemia, Ann. Surg. **105**:354 (March) 1937. (*u*) Lukens, F. W., and Ravdin, I. S.: Adenoma of the Islet Cells of the Pancreas with Operation and Recovery, Am. J. M. Sc. **194**:92 (July) 1937. (*v*) Cragg, R. W.; Power, M. H., and Lindem, M. C.: Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism, Arch. Int. Med. **60**:88 (July) 1937.

7. McClenahan, W. U., and Norris, D. W.: Adenoma of the Islands of Langerhans with Associated Hypoglycemia, Am. J. M. Sc. **177**:93 (Jan.) 1929.

8. Terbrüggen, A.: Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome, Beitr. z. path. Anat. u. z. allg. Path. **88**:37 (Nov. 19) 1931.

*C. Pathologic Observations.*—In cases of spontaneous hypoglycemia due to neoplasm or to hyperplasia or hypertrophy of the islands of Langerhans little pathologic change was observed in other organs of the body. In most instances the liver was essentially normal. Changes in the central nervous system have been reported in only a few cases of proved islet cell neoplasm. These consisted of cerebral edema and congestion (Thalheimer and Murphy,[9]), perivascular round cell infiltration in the meninges and brain (McClenahan and Norris [7]), atrophy of the cortex and fatty degeneration of the ganglion cells (Terbrüggen [8]), moderate diffuse loss of ganglion cells from the cortex (Wolf and his associates [6h]) and scattered hemorrhages (Baker and Lufkin [10]).

For several patients who died in "insulin shock," cerebral changes have been reported. Macroscopically, Wohlwill [11] described a dry friable brain; other authors (Bowen and Beck,[4] Bodechtel [12] and de Morsier and Mozer [13]) noted cerebral edema. The histologic changes varied from moderate to severe diffuse degeneration of the ganglion cells in the cortex and basal ganglions. Bodechtel [12] emphasized the focal occurrence of the changes and the prevalence of Spielmeyer's "homogeneous cell disease" in his case. Others (Wohlwill [11] and Terplan [14]) described "Nissl's severe change" in the neurons and swelling phenomena of the glia and axis-cylinders.

Experimentally, a number of investigators were able to produce definite pathologico-anatomic changes by induced hyperinsulinism. Schereschewsky and his co-workers [15] noted necrosis in the adrenal glands; lipoidosis of the liver and kidneys; generalized edema, congestion and hemorrhages, and degeneration of the neurons in the sympathetic and central nervous systems. The authors placed particular emphasis on the changes in the sympathetic system. According to Stief

9. Thalheimer, W., and Murphy, F. D.: Carcinoma of Islands of Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **91**:89 (July 14) 1928.

10. Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190 (Feb.) 1937.

11. Wohlwill, F.: Ueber Hirnbefunde bei Insulin-Ueberdosierung, Klin. Wchnschr. **7**:344 (Feb. 19) 1928.

12. Bodechtel, G.: Der hypoglykämische Schock und seine Wirkung auf das Zentralnervensystem zugleich ein Beitrag zu seiner Pathogenese, Deutsches Arch. f. klin. Med. **175**:188, 1933.

13. de Morsier, G., and Mozer, J. J.: Lésions cérébrales mortelles par hypoglycémie au cours d'une traitement insulinique chez un morphinomane, Ann. de méd. **39**:474 (May) 1936.

14. Terplan, K.: Changes in the Brain in a Case of Fatal Insulin Shock, Arch. Path. **14**:131 (July) 1932.

15. Schereschewsky, N. A.; Mogilnitzky, B. N., and Gorjaewa, A. W.: Zur Pathologie und pathologischen Anatomie der Insulinvergiftung, Endokrinologie **5**:204, 1929.

and Tokay,[16] both diffuse and focal types of parenchymatous degeneration can be produced in the cortex and basal ganglions, the severity and the acuteness of the changes being directly proportional to the dosage of insulin and the duration of its administration. Similar pathologic observations were reported by Grayzel,[17] who said he believed that the severity of the changes depended on the frequency and intensity of the convulsions.

*D. Pathogenesis.*—Regarding the mechanism of injury to the central nervous system, opinions differ as to whether the hypoglycemia, the insulin per se or other disturbances of metabolism are the responsible factors. On the basis of experimental data, two theories have been postulated: (1) anoxemia and (2) disturbed water balance.

1. Theory of Anoxemia: Olmsted and Logan,[18] in an early report, observed that the arterial blood in insulin hypoglycemia was venous in character, and they compared the effects of hyperinsulinism to those of asphyxia. They assumed that "anoxemia of the brain through a depressant effect of the hypoglycemia" was responsible for the convulsions. Dameshek, Myerson and Stephenson[19] arrived at similar conclusions after obtaining by the "internal jugular method" during a severe insulin reaction a marked diminution in the normal arteriovenous difference in the content of oxygen, signifying a reduction in the uptake of oxygen by the brain. However, in a later study, Olmsted and Taylor[20] found that after the administration of insulin there is only a slight fall in the oxygen saturation of the arterial blood preceding the convulsion. They concluded that the convulsions cannot be attributed to the "mild anoxemia" but that both phenomena are directly caused by the insulin.

2. Theory of Disturbed Water Balance: Drabkin and Ravdin[21] reported that in previously dehydrated animals, insulin in doses suffi-

16. Stief, A., and Tokay, L.: Beiträge zur Histopathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434, 1932; Weitere experimentelle Untersuchungen über die cerebrale Wirkung des Insulins, ibid. **153**:561, 1935.

17. Grayzel, D. M.: Changes in the Central Nervous System Resulting from Convulsions Due to Hyperinsulinism, Arch. Int. Med. **54**:694 (Oct.) 1934.

18. Olmsted, J. M. D., and Logan, H. D.: Effect of Insulin on the Central Nervous System and Its Relation to the Pituitary Body, Am. J. Physiol. **66**:437 (Oct.) 1923.

19. Dameshek, W.; Myerson, A., and Stephenson, C.: Insulin Hypoglycemia, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935.

20. Olmsted, J. M. D., and Taylor, A. C.: Effect of Insulin on the Blood: Changes in Oxygen Saturation, Percentage Hemoglobin and Oxygen Capacity, Am. J. Physiol. **69**:142 (June) 1924.

21. Drabkin, D. L., and Ravdin, I. S.: The Mechanism of Convulsions in Insulin Hypoglycemia, Am. J. Physiol. **118**:174 (Jan.) 1937.

cient to cause hypoglycemia failed to produce convulsions or to influence the pressure of the cerebrospinal fluid. On the contrary, in previously hydrated animals a rise in the pressure of the cerebrospinal fluid and in the incidence of convulsions regularly occurred. The authors concluded that insulin convulsions occur only when the sequence of hypoglycemia, anhydremia and a rise in the pressure of the cerebrospinal fluid takes place and said they considered the anhydremia as the most important factor in the mechanism of the convulsions.

Comment: These theories have been applied to explain the anatomic changes in the nervous system. Thus, Bowen and Beck [4] interpreted their findings of cerebral edema as an effect of anhydremia in the sense accepted by Drabkin.[21] Other authors have attributed the changes to the hypoglycemia either directly through diminished nutrition (Terbrüggen,[8] and Wolf, Hare and Riggs [6h]) and the anoxemia effect on the brain tissue or indirectly by causing vasospasm in the sense accepted by Spielmeyer (Bodechtel,[12] Stief and Tokay,[16] Grayzel [17] and de Morsier and Mozer [18]). Thus, Bodechtel [12] compared the histologic picture with changes produced by ligating the carotid arteries and with other "circulatory disturbances." He attributed the focal lesions, the type of neuronal alteration ("homogeneous cell disease") and the occasional capillary hemorrhages to spasm or stasis of the blood vessels. According to Stief and Tokay,[16] pathologic changes in the brain can be produced experimentally only by subcutaneous and cisternal but not by intracerebral injections of insulin. This the authors said they regarded as proof for the vascular action of the hypoglycemia, as opposed to a direct irritant effect of the insulin. Schereschewsky and his associates [15] suggested that the mechanism is partly vasomotor through changes in the sympathetic system and partly a direct toxic action of insulin on the central nervous system. Wohlwill [11] attributed the cerebral changes to alkalosis.

## GENERAL COMMENT

Our case represents a typical example of hyperinsulinism due to islet cell adenoma. The clinical course of convulsive attacks, focal neurologic signs and atypical psychotic manifestations demonstrates the variability in the symptomatology in such cases. Certain clinical features that have not been sufficiently emphasized in the literature are significant. It has been generally regarded that the episodic course of the symptoms is characteristic of the disorder. In our case, however, this initial phase was gradually replaced by permanent organic dementia. Again, the relief of symptoms with the elevation of the blood sugar to normal or higher levels, so characteristic of this condition, was not found in our case. It seems reasonable to believe that in the initial phases of the disease the pathologic effects are of a reversible order and can be relieved by dietary or surgical therapy. With the progress of the dis-

order, however, permanent impairment of cerebral functioning that is no longer amenable to therapy may take place. This is corroborated in our case by the pathologico-anatomic changes.

The extremely variable results of the reported laboratory tests,[22] as reviewed, make their interpretation difficult. In attempting to explain the paradoxical dextrose tolerance curves, Weil [22j] stated the opinion that the curve varies with the type of lesion in the pancreas. Thus, he concluded that the high, almost diabetic curve is characteristic of carcinoma of the islet cells, that the moderately high and prolonged curve is suggestive of adenoma and that the low, flat curve is typical of "functional" hyperinsulinism when there are no demonstrable structural changes. Feiner and his associates [6n] said they regarded the plateau type of curve as characteristic of islet cell adenoma. However, further analysis reveals that such a relation is not consistent. Table 4 shows that

22. (*a*) Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 26) 1924; Hyperinsulinism and Dysinsulinism (Insulogenic Hypoglycemia) with Chronological Review of Cases Reported in the United States and Canada, Endocrinology **16**:29 (Jan.-Feb.) 1932; Hyperinsulinism, a Definite Disease Entity: Etiology, Pathology, Symptoms, Diagnosis, Prognosis, and Treatment of Spontaneous Insulogenic Hypoglycemia (Hyperinsulinism), J. A. M. A. **101**:1958 (Dec. 16) 1933; Epilepsy and Narcolepsy Associated with Hyperinsulinism, ibid. **100**:321 (Feb. 4) 1933; Clinical Types of Hyperinsulinism: Case Reports, Am. J. Digest. Dis. & Nutrition **1**:562 (Oct.) 1934. (*b*) Nielsen, J. M., and Eggleston, E. L.: Functional Dysinsulinism with Epileptiform Seizures; Treatment, J. A. M. A. **94**:860 (March 22) 1930. (*c*) Winans, H. M.: Chronic Hypoglycemia, South. M. J. **23**:402 (May) 1930. (*d*) Waters, W. C., Jr.: Spontaneous Hypoglycemia: The Role of Diet in Etiology and Treatment, ibid. **24**:249 (March) 1931. (*e*) Marsh, H. E.: Hyperinsulinism, with Report of a Case, Wisconsin M. J. **30**:340 (May) 1931. (*f*) Gammon, G. D., and Tenery, W. C.: Hypoglycemia: Clinical Syndrome, Etiology and Treatment: Report of a Case Due to Hyperinsulinism, Arch. Int. Med. **47**:829 (June) 1931. (*g*) Moore, H.; O'Farrell, W. R.; Malley, L. K., and Moriarity, M. A.: Acute Spontaneous Hypoglycemia, Brit. M. J. **2**:837 (Nov. 7) 1931. (*h*) Shepardson, H. C.: Glycopenia: The Efficacy of High Fat Diets in the Treatment of Chronic Hypoglycemia, Endocrinology **16**:182 (March-April) 1932. (*i*) McGovern, B. E.: Epileptoid Attacks and Hyperinsulinism: Report of a Case, ibid. **16**:293 (May-June) 1932. (*j*) Weil, C. K.: Functional Hyperinsulinism: Epileptiform Convulsions, Accompanying Spontaneous Hypoglycemia, Internat. Clin. **4**:33 (Dec.) 1932. (*k*) Sippe, C., and Bostock, J.: Hypoglycemia: A Survey and an Account of Twenty-Five Cases, M. J. Australia **1**:207 (Feb. 18) 1933. (*l*) Graham and Womack.[6g] (*m*) Tedstrom, M. K.: Hypoglycemia and Hyperinsulinism, Ann. Int. Med. **7**: 1013 (Feb.) 1934. (*n*) Clark, B. B., and Greene, J. A.: Effect of Low Carbohydrate Diet on the Glucose Tolerance in Spontaneous Hypoglycemia, Proc. Soc. Exper. Biol. & Med. **32**:1459 (June) 1935. (*o*) Powell, E.: The Story Behind Two Blood Sugar Curves (Hypoglycemia as a Cause of Mental Symptoms), Tri-State M. J. **8**:1612 (March) 1936. (*p*) McCullagh, E. P.: Treatment of Chronic Hypoglycemia, M. Clin. North America **19**:2005 (May) 1936. (*q*) MacBryde, C. M.: Borderline Endocrine Disturbances, ibid. **20**:337 (Sept.) 1936.

there were five instances of the low type of curve in cases of proved islet cell neoplasm, two instances of the high type of curve in cases in which a normal pancreas was seen at operation and six instances of the high curve in cases of functional hyperinsulinism.

We believe that the type of dextrose tolerance curve furnishes an index of the degree of the severity of the disorder, regardless of the

TABLE 4.—*Summary of Data on Dextrose Tolerance Curves Reported in Literature*

| Etiologic Factor | Dextrose Tolerance Curves, Number of Cases | | | Epinephrine Response, Number of Cases | |
|---|---|---|---|---|---|
| | High | Low | Unclassified | Adequate | Inadequate |
| 1. Neoplasms of islet cells * | 21 | 5 | 1 | 12 | 3 |
| 2. Hypertrophy or hyperplasia of islet cells † | .. | 3 | 1 | .. | .. |
| 3. Resection of normal pancreas ‡ | 2 | 7 | .. | 3 | .. |
| 4. Functional hyperinsulinism § | 6 | 53 | .. | 7 | 1 |

* Footnote 6.
† Simon, H. E.: Surgery in the Treatment of Hyperinsulinism, South. Surgeon **3**: 211 (Sept.) 1934. McCaughan and Broun.[6t]
‡ Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Tr. Am. S. A. **46**: 268, 1928; Ann. Surg. **88**: 584 (Sept.) 1928. Harris, S.: Epilepsy and Narcolepsy Associated with Hyperinsulinism, J. A. M. A. **100**: 321 (Feb. 4) 1933; The Diagnosis of Surgical Hyperinsulinism, South. Surgeon **3**: 199 (Sept.) 1934; Clinical Types of Hyperinsulinism: Case Reports, Am. J. Digest. Dis. & Nutrition **1**: 562 (Oct.) 1934. Holman, E., and Railsback, O. C.: Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia, Surg., Gynec. & Obst. **56**: 501 (March) 1933. Graham, E. A., and Hartmann, A. F.: Subtotal Resection of the Pancreas for Hypoglycemia, ibid. **59**: 474 (Sept.) 1934. McCaughan and Broun.[6t] Womack, N. A., and Cole, W. H.: The Thyroid Gland in Hypoglycemia, Ann. Surg. **105**: 370 (March) 1937.
§ Footnote 22.

TABLE 5.—*Relation of Dextrose Tolerance Curve to Severity of Disorder*

| Etiologic Factor | Symptoms | Number of Cases | Dextrose Tolerance Curve | | |
|---|---|---|---|---|---|
| | | | High | Low | Unclassified |
| Neoplasm | Severe | 23 | 21 | 1 | 1 |
| | Mild | 4 | .. | 4 | |
| Hypertrophy and hyperplasia | Mild | 4 | .. | 3 | 1 |
| Resection of normal pancreas | Severe | 2 | 2 | | |
| | Mild | 7 | .. | 7 | |
| Functional hyperinsulinism | Severe | 7 | 6 | 1 | |
| | Mild | 52 | .. | 52 | |
| Total | Severe | 32 | 29 | 2 | 1 |
| | Mild | 67 | .. | 66 | 1 |

type of lesion in the pancreas. In table 5 an attempt has been made to illustrate such a relation. Here the same dextrose tolerance tests recorded in table 4 are tabulated in relation to the type of symptom found in each instance, the symptoms being arbitrarily classified as severe or mild. The severe type of disorder is characterized by frequently recurring convulsions, prolonged periods of coma and other severe neuropsychiatric symptoms or requires dextrose therapy approximately every two hours to prevent attacks. In such cases the dextrose tolerance curve is predominantly of the high type. In the milder form

the symptoms consist of fleeting periods of unconsciousness or abnormal behavior. The relief obtained from dextrose is of longer duration. Convulsions are not prominent, but occasionally hypoglycemia may precipitate a latent convulsive disorder. In these cases in which the symptoms are mild the dextrose tolerance curve is consistently of the low or flat type.

The factors underlying these curves are complex and still obscure. It is known that the high type of dextrose tolerance curve is also characteristic of hypoglycemia resulting from hepatic disease or from experimental extirpation of the liver. Further, it is obtained also with starvation or with a diet low in carbohydrate, when it is attributed more clearly to a depletion of the hepatic glycogen. These facts suggest that the high and diabetic types of dextrose tolerance curves in cases of severe hyperinsulinism point to a complicating hepatic factor which would at least partially explain the otherwise unexpected high curve. This is to be understood in the sense of physiologic disturbance rather than as actual structural change in the liver. The latter is usually lacking, as in our case. Hepatic function tests and the response to epinephrine in hyperinsulinism vary considerably and frequently fail to indicate involvement of the liver or the adequacy of glycogen storage. In our case, for example, in which the response to epinephrine was adequate and hepatic function tests gave normal results, the glycogen content was markedly diminished, even though this may have been partly caused by the terminal increased metabolism associated with the fever before death. An evaluation of these findings is as yet impossible, in view of the paucity of reports of hepatic glycogen determinations in the literature. In the few reports available, the glycogen content was said to be either adequate or greatly diminished. The question still remains whether in severe hyperinsulinism the liver is depleted of glycogen or whether the glycogen is so firmly fixed in the liver by the excess insulin that a normal response to ingestion of dextrose is not obtained. On the other hand, in cases of milder hyperinsulinism, in which the curve is low or flat, one can picture an insulin-liver mechanism which is overworking in much the same manner as it does in response to the stimulus of increased intake of carbohydrate (Sweeney [23] and Himsworth [24]). The flat type of curve is also obtained at times in cases of hypo-adrenalism, hypothyroidism and hypopituitarism in which there is a normal insulin-secreting mechanism but a diminished concentration of insulin antagonists. One can consider that in these cases there is mild relative hyperinsulinism associated with the fundamental disease.

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23. Sweeney, J. S.: Dietary Factors That Influence the Dextrose Tolerance Test: A Preliminary Study, Arch. Int. Med. **40**:818 (Dec.) 1927.

24. Himsworth, H. P.: Dietetic Factor Determining Glucose Tolerance and Sensitivity to Insulin of Healthy Men, Clin. Sc. **2**:67 (Sept.) 1935.

Thus, it is suggested that the response to ingestion of dextrose in the cases of mild involvement is that of a well coordinated overactive mechanism, while in the severe forms, in which there is a high type of curve, the insulin-liver mechanism is functioning incoordinately. Our case, in which there were a consistently high type of dextrose tolerance curve and marked depletion of the hepatic glycogen, serves to illustrate the latter and is clearly correlated with the severe clinical and pathologico-anatomic conditions.

The anatomic basis for the clinical manifestations in our case is evident in the advanced destruction of the cortex, thalamus and striatum. The greater involvement of the left cerebral hemisphere apparently accounts for the contralateral jacksonian attacks. This is a unique example of severe pathologic effects on the brain in a case of hyperinsulinism. The outstanding feature of the anatomic changes is their purely parenchymatous degenerative character. All the characteristics of a primary toxic degenerative process are obvious from the direct and diffuse effect on the parenchyma, beginning with "acute swelling" of the neurons and paling of the tissue and progressing to ultimate degeneration, to which the glia reacts secondarily. The condition is analogous to primary degenerative diseases of the central nervous system and to encephalopathies due to exogenous toxins (for instance, morphine or nitrous oxide). It suggests a direct toxic effect of some substance elaborated in hyperinsulinism. One may speculate here about the possibility that the excess insulin in the blood may act as such a toxic substance.

In view of the complexity of insulin metabolism, such an assumption is supported mainly by indirect evidence. For, as previously mentioned, the phenomena of hypoglycemia, anoxemia, anhydremia, alkalosis and other metabolic disturbances accompanying hyperinsulinism have been held responsible for the cerebral changes. It remains to be seen whether any of these are the essential factors in this disorder and are capable of producing such pathologic effects on the brain.

The primary role attributed to the hypoglycemia has been questioned in view of the lack of parallelism between the level of the blood sugar and the clinical manifestations. It is also known that drugs which have no appreciable effect on the blood sugar level can be used therapeutically as antidotes in insulin shock (Popper and Jahoda [25]). The cerebral changes which have been attributed to the hypoglycemia, on the assumption of either its vasospasmodic action or its anoxemic effect, cannot be confirmed here. While both diffuse and focal changes have been observed in animal experimentation and in cases of fatal

25. Popper, L., and Jahoda, S.: Coffeinwirkung bei hypoglykämischen Zuständen, Klin. Wchnschr. **9**:1585 (Aug. 23) 1930.

insulin shock, undue emphasis has been placed on the focal changes and the entire condition attributed to vascular spasm, in the sense accepted by Spielmeyer. It seems to us that these changes are merely local accentuations of the diffuse process. In our case the characteristics of such vasomotor disturbances as discontinuous focal areas of necrosis and ischemic changes in the nerve cells are entirely lacking. In the cornu ammonis the resistant part is degenerated, not Sommer's sector, as would be expected in vascular conditions. Moreover, the widespread laminar distribution of the degeneration cannot be attributed to vascular factors (Braunmühl [26]). Also, changes in the electrocardiogram, pulse rate and blood pressure in this disorder are said to confirm a vascular etiology. However, it is still disputed whether these cardiovascular effects are produced by the hypoglycemia or by insulin toxicity (Hadorn [27]).

For similar morphologic reasons, comparisons with cerebral anoxemia are untenable. As outlined by Gildea and Cobb,[28] the pathologic picture of acute cerebral anoxemia following ligation of the carotid arteries consists predominantly of necrobiotic foci and characteristic changes in the ganglion cells (shrunken cells, cells with spikelike processes). In chronic anoxemia the white matter, because of its lower consumption of oxygen, is more involved than the gray matter (Putnam [29]), whereas in this disorder the white substance is spared. Undoubtedly, impaired oxidation of the brain accompanies the hypoglycemia, but this does not explain the clinical manifestations (Olmsted and Taylor [20]) nor the histopathologic changes.

It seems unlikely that hydration of the central nervous system (in the sense of Drabkin) can produce such a clinicopathologic picture. For, although the experiments of Drabkin and Ravdin [21] demonstrate a relation between convulsions and anhydremia induced by insulin, other clinical manifestations remain unexplained. Pathologico-anatomically, one would expect that cerebral edema would be more frequent in hyperinsulinism than is actually the case. Moreover, it is doubtful whether edema can produce such degeneration of nerve tissue.

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26. Braunmühl, A. V.: Picksche Krankheit, in Bumke, O.: Handbuch der Geisteskrankenheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

27. Hadorn, W.: Das Herz in Insulinschock, Schweiz. med. Wchnschr. **39**: 936 (Sept.) 1936.

28. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

29. Putnam, T. J.: The Cerebral Circulation: Some New Points in Its Anatomy, Physiology and Pathology, J. Neurol. & Psychopath. **17**:193 (Jan.) 1937.

SUMMARY

A case of chronic hypoglycemia due to an islet cell adenoma of the pancreas is reported, with clinical laboratory and pathologico-anatomic data.

The clinical course of convulsions, psychotic manifestations and organic dementia is correlated with the advancing destruction of the cerebral cortex and basal ganglions.

The diffuse degeneration of the brain is interpreted as a direct toxic effect of insulin on the parenchyma.

It is suggested that the dextrose tolerance test in cases of hyperinsulinism is an index of the severity of the pathologico-physiologic process. This is to be understood as a change in the insulin-liver mechanism regulating dextrose metabolism.

# CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS

## IV. OBLITERATING PULMONARY ARTERITIS WITH SECONDARY PULMONARY CHANGES AND RIGHT VENTRICULAR HYPERTROPHY; REPORT OF A CASE WITH AUTOPSY

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AND
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NEW YORK

Thrombo-angiitis obliterans, or Buerger's disease, is a well recognized clinical entity. In the majority of cases the condition is localized in one group of arteries,[1] but in some cases it may even invade neighboring veins, in the form of phlebitis migrans. Obliterating arteritis, on the other hand, is confined to the smallest arterioles, without involvement of the venous system. Hence, these two conditions must be considered apart pathologically and clinically.

Despite the fact that obliterating arteritis is a rare disease, the recent clinical significance attributed to it warrants reporting a case in which we have had the opportunity of following the disease from onset to termination.

### REPORT OF CASE

D. P., a man aged 33, experienced sudden pain in the chest, with dyspnea, six months before admission to the hospital. He consulted his family physician, but the only objective findings were tachypnea and tachycardia. He continued to work, with periodic confinement to bed, until he had lost 20 pounds (9 Kg.) and had become so weak that he was no longer able to continue in his occupation.

On Jan. 8, 1934, he was seen by his family physician in consultation with Dr. I. W. Held, and he said that although he experienced pain in the chest on exertion, this was not as troublesome as the shortness of breath. The chief findings were tachypnea, tachycardia, moderate cyanosis of the lips and fingers

† Dr. Rothschild died on Feb. 16, 1936.

Aided through the Henry Dazian Fund.

From the Department of Medicine and the Department of Pathology, the Beth Israel Hospital.

1. (*a*) Birnbaum, Walter; Prinzmetal, Myron, and Connor, Charles L.: Generalized Thrombo-Angiitis Obliterans: Report of a Case with Involvement of the Retinal Vessels and Suprarenal Infarction, Arch. Int. Med. **53**:410 (March) 1934. (*b*) Horton, Bayard T.; Magath, Thomas B., and Brown, George E.: Arteritis of the Temporal Vessels, ibid. **53**:400 (March) 1934.

without clubbing and a rapid pulse. The eyes were staring, but the blood pressure was not increased. There was no orthopnea. Examination of the chest revealed a few sibilant rales at the bases of the lungs, with diminished breathing over the base of the left lung. On auscultation a split first sound and an accentuation of the pulmonic second sound were noted. Fluoroscopic examination showed the apex of the heart in the midclavicular line. The pulmonary artery was not dilated. Over the base of the left lung there was a dense area suggestive of pneumonitis, and the left interlobar pleura was thickened, with restriction of diaphragmatic movement on the left. In the second oblique position there was density in the midportion of the retrosternal space suggestive of thickening of the mediastinal pleura.

The diagnosis seemed to lie between coronary thrombosis (sine dolore), with an infarct in the left ventricle, and a mediastinal mass (Hodgkin's disease) pressing on the vagus nerve. Of the two conditions, it seemed more likely that the former was the cause of the patient's symptoms, particularly in view of the thickened pleura and the strong suggestion of a secondary pulmonary infarct. The absence of glandular enlargement did not favor a diagnosis of Hodgkin's disease of the thorax.

On January 11 the patient entered the hospital on the service of one of us (Dr. Rothschild). The symptoms and physical findings were unchanged except that the heart sounds gave an impression of a gallop rhythm. However, a phonocardiogram showed only a split first sound and no true gallop rhythm.

*Laboratory Data.*—The blood count showed 16,900 leukocytes, with 81 per cent segmented cells. The red blood cell count and the hemoglobin values were normal. The sedimentation rate was 27 and 45 per cent, respectively, on two occasions. Chemical analysis of the blood showed 35 mg. of lactic acid per hundred cubic centimeters (increased). The calcium and phosphorus values were normal.

The basal metabolic rate was 37 and 27 per cent, respectively, on two occasions.

A cardiodynamic study revealed the following: venous pressure, 4 cc.; circulatory time (saccharine method), thirteen seconds; plasma volume, 2,813 cc.; total blood volume, 5,228 cc.; oxygen consumption, 300 cc.; arteriovenous oxygen difference (calculated from the dissociation curves of the blood), 50 cc.; cardiac output, 6 liters (calculated value, 4.82 liters),[2] and vital capacity, 2,300 cc.

The oxygen dissociation curve was normal, with marked diminution of the saturation of blood starting at about 8 volumes per cent and dropping to 3 volumes per cent (fig. 1). The arterial oxygen saturation was 50 per cent of normal (figs. 2 and 3).

The electrocardiographic study showed a regular rhythm of 100 beats per minute, a normal P R interval, a diphasic $T_1$ wave, a diphasic $T_2$ wave and an abnormal lead IV, in that there was an upright $T_4$ wave (anteroposterior method). These findings suggested myocardial damage (fig. 4).

Roentgenographic study of the chest by Dr. I. Seth Hirsch revealed diffuse interstitial changes involving both lungs and not associated with the marked congestion. The pleura of the middle and lower lobes of the right lung was

2. The increased cardiac output (6 liters) is of no significance because of the marked tachypnea and the difficulty with which the alveolar samples were collected. The true value of the cardiac output calculated from the blood volume showed no increase (Goldbloom, A. Allen, and Roht, Paul K.: Cardiac Output Values from Calculated Blood Volume, unpublished data).

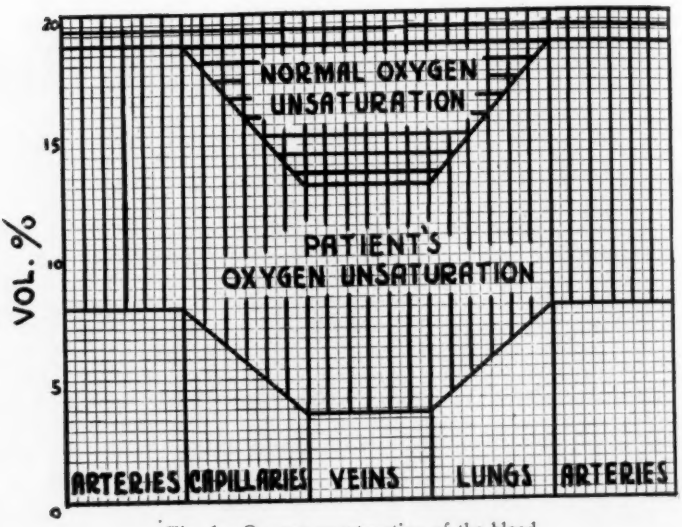


Fig. 1.—Oxygen unsaturation of the blood.

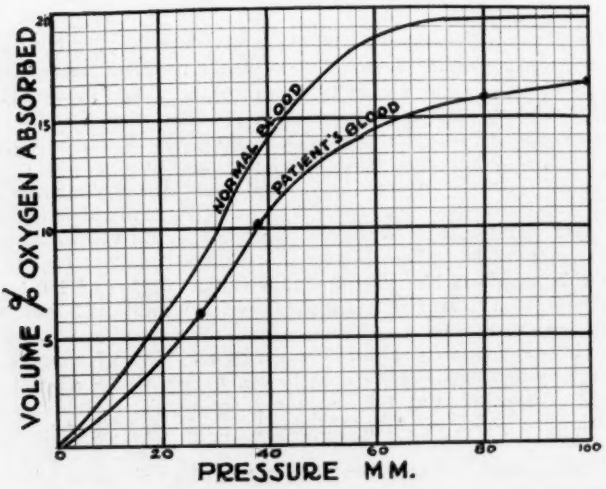


Fig. 2.—Oxygen dissociation curve. The carbon dioxide pressure was 40 mm.

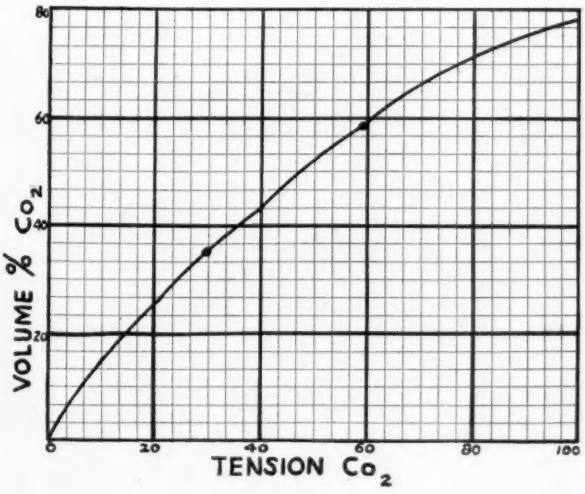


Fig. 3.—The carbon dioxide absorption curve for oxygenated whole blood.

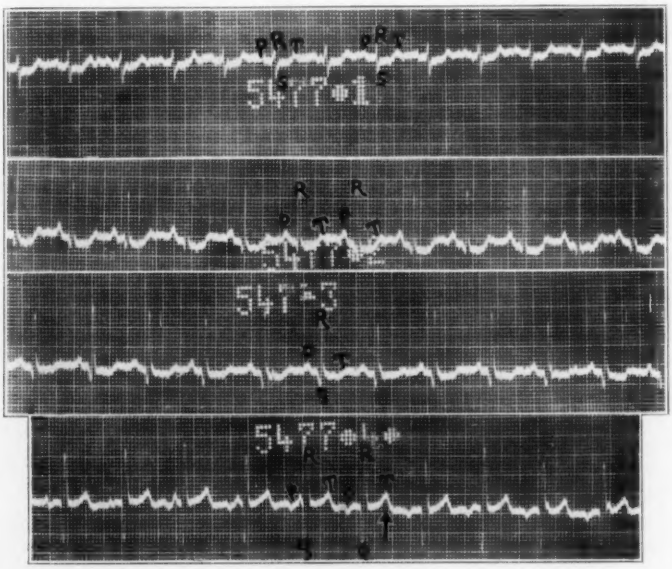

Fig. 4.—Electrocardiographic tracings.

markedly thickened, and there was a small amount of effusion in the pleural cavity. The left ventricle was enlarged. The mediastinum was normal. The most striking features were the diffuse congestion and the interstitial changes in the lower lobe of the right lung.

Roentgenograms of the phalanges showed no periosteitis or thickening of the soft tissues.

Bronchoscopic examination by Dr. J. Miller revealed no abnormality.

*Diagnosis.*—Although there was electrocardiographic evidence of myocardial damage (fig. 4), the cardiodynamic studies (normal blood volume and circulatory time) tended to rule out a coronary condition as the direct cause of the myocardial damage. Hodgkin's disease was finally ruled out by the normal roentgenographic and bronchoscopic findings. Thyrotoxicosis, likewise, was eliminated as a possibility by the fact that the blood volume, circulatory time and cardiac output were not increased, as they usually are in this condition.[3]

On the basis of the clinical picture, namely, cyanosis, tachycardia, tachypnea and no orthopnea (closely resembling the symptoms in the case reported by Frothingham[4]) and also because of the diminished oxygen saturation, indicating some obstruction in the arterial system, the condition was diagnosed (by Dr. Rothschild) as due to an infection, with primary involvement of the pulmonary arterioles.

*Progress.*—The tachypnea and cyanosis continued. The temperature rose to 101 F., the pulse rate was 120 and the respiratory rate was 44. Evidence of failure of the right side of the heart increased. Oxygen and digitalis treatment were of no avail. Two days before death occurred pulmonary edema developed with acute failure of the left ventricle. The patient died on February 4, three weeks after admission to the hospital.

*Gross Postmortem Examination.*[5]—The postmortem diagnosis was obliterating arteritis of the small pulmonary arteries, partly thrombo-arteritis; dense pleural adhesions, and hypertrophy of the right ventricle.

The pericardium was normal. The pulmonary arteries were free. The right side of the heart was distinctly hypertrophied. The coronary arteries were normal.

In the middle of the upper lobe of the left lung there was a firm, round, irregularly outlined mass directly beneath the pleura. The latter was thickened and hyperemic. The interlobar space was obliterated. Another firm indefinitely circumscribed area was situated near the lower edge. No distinct circumscribed lesions were seen in the pulmonary artery. Incision of the lungs revealed a number of

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3. Goldbloom, A. Allen: Diagnostic Importance of Blood Volume and Cardiac Output Studies in a Borderline Case of Thyrotoxicosis, M. Clin. North America **17**:279, 1933. Goldbloom, A. Allen; Libin, I., and Roht, Paul K.: Clinical Studies in Circulatory Adjustments: I. Clinical Evaluation of Studies of Circulating Blood Volume, Arch. Int. Med. **55**:484 (March) 1935. Goldbloom, A. A., and Bauer, Herman E.: II. Venous Pressure, a Simple Bedside Method, in Collected Papers of the New York Homeopathic Medical College and Flower Hospital, 1935, vol. 5, pp. 45-52. Goldbloom, A. Allen, and Roht, P. K.: III. Clinical Evaluation of Cardiac Output Studies, Internat. Clin. **3**:206, 1936.

4. Frothingham, Channing: A Case of Extensive Bilateral Progressive Thrombosis of the Smaller Branches of the Pulmonary Arteries, Am. J. Path. **5**:11, 1929.

5. A detailed pathologic study is to be reported elsewhere by Dr. Alfred Plaut, pathologist for the Beth Israel Hospital.

grayish white, round and oblong spots adhering to some cylindric structures corresponding to the obliterated vessels. Further incision revealed additional dark red thrombi.

*Microscopic Postmortem Examination.*—The gray foci observed grossly proved to be completely obliterated blood vessels. In most cases the lumen was entirely filled with rather cellular fibrous tissue, with larger or smaller spaces of recanaliza-

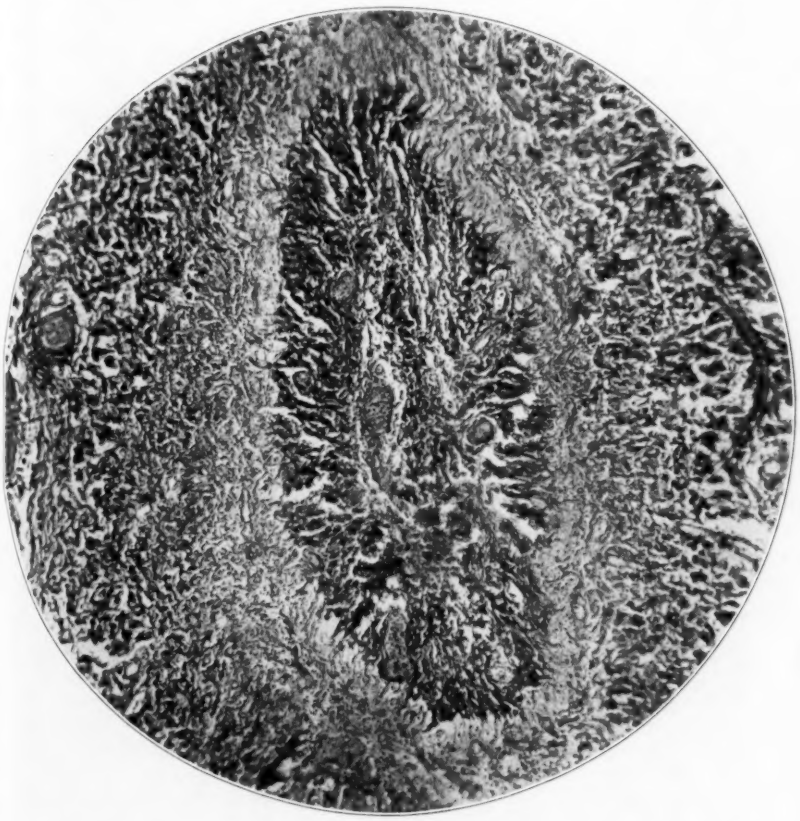

Fig. 5.—Microscopic section showing a completely fibrosed artery of the lung, with obliteration of the lumen; Van Gieson stain.

tion. True inflammatory lesions were present in only a few places, represented by rather uncharacteristic granulation tissue, in which, however, giant cells were conspicuous. The thrombosed vessels observed grossly appeared to be intact. Some arteries showed an obviously inflammatory overgrowth of intima. In these vessels the intimal cells had large nuclei. Other arteries, again, had a small, regular intimal overgrowth without any evidence of inflammation. In a large number of obliterated arteries no remnants of thrombotic material were observed. The myocardium contained granulation tissue and scars (fig. 5).

COMMENT

Eppinger and Wagner [6] reported eight cases of primary arteriolar disease, with invasion of the small pulmonary vessels, producing circulatory failure. Careful analysis, however, reveals that in only two cases was there true obliterating arteritis. In the others there was primary vascular disease, with characteristics of either thrombo-angiitis or obliterative sclerotic arteriolar disease.

Cases similar to the one herein described have been reported recently by Frothingham,[4] MacCallum,[7] and Waring and Black.[8] The patient reported on by Frothingham was seen by one of us (Dr. Rothschild). Pathologic examination showed that all the pulmonary arteriolar branches were completely occluded by thrombi, the smallest branches showing primary acute lesions and a condition simulating thrombo-angiitis obliterans.

There is growing interest in the consideration of primary arterial disease, particularly notable being a series of articles recently published by Brenner.[9]

Circulatory failure of an extracardiac nature, due to pulmonary emphysema, kyphoscoliosis, Ayerza's disease [1b] or hypertension, or secondary to sclerosis of the larger arteries, is of frequent occurrence. Likewise, sclerosis of the pulmonary arterioles, with sclerosis of the pulmonary artery with or without general arteriosclerosis, is not uncommon as a cause of circulatory failure of extracardiac origin. Many years ago von Neusser called attention to the fact that in these cases there is marked dyspnea even on slight exertion, producing symptomatic polycythemia or cyanosis, giving cause for suspicion of sclerosis not only of the pulmonary artery but of the arterioles and capillaries as well, leading to fibrosis of the pulmonary alveoli and producing status volumen pulmonum auctum, with eventual failure of the right side of the heart. More recently, Moschcowitz [10] and Miller [11] have shown that sclerosis of the pulmonary artery, with or without involvement of the smaller

6. Eppinger, Hans, and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. f. inn. Med. **1**:83, 1920.

7. MacCallum, W. G.: Obliterative Pulmonary Arteriosclerosis, Bull. Johns Hopkins Hosp. **49**:37, 1931.

8. Waring, James J., and Black, W. C.: Syndrome of Obstruction in Lesser Circulation, Am. J. M. Sc. **187**:652, 1934.

9. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:211 (Aug.); 457 (Sept.); 724 (Oct.); 976 (Nov.); 1189 (Dec.) 1935.

10. Moschcowitz, Eli: The Cause of Arteriosclerosis, Am. J. M. Sc. **178**:224 (Aug.) 1929.

11. Miller, H. R.: Sclerosis of Pulmonary Artery and Its Branches, M. Clin. North America **9**:673 (Nov.) 1925.

vessels, is not uncommon. The symptom complex which goes under the name cor pulmonale and which is due to the cause mentioned has long been recognized. However, obliterating arteritis of the small pulmonary vessels leading to cardiac failure (cor pulmonale) deserves emphasis because of its rarity.

In the few cases of localized obliterating arteritis reported in the literature the pulmonary lesion showed extensive fibrosis of the alveolar septums, many being almost avascular, with a peculiar peribronchial and perivascular increase in connective tissue. In addition, there were thrombosis and complete obliteration of the smaller arteries and in some cases infarction of the lungs.

As yet, the etiologic factor in obliterating arteritis of the pulmonary arterioles is undetermined. It is well known that infarction can cause arteritis or periarteritis nodosa and that the rheumatic virus has a marked affinity for the pulmonary vessels. But in the case reported herein there was no evidence of either a generalized or a rheumatic infection (the latter was ruled out by the absence of Aschoff bodies).

Judging from the onset of symptoms in the cases that have been reported and in our case, there is a possibility that allergy may play a role. This concept is based on the following supposition: Since it is known that all allergic manifestations, from the severest anaphylactic shock followed by death to chronic allergy, are characterized by spasm of the small arterioles and capillaries, it is possible that the first attack described by the patient, in which he suffered shortness of breath while walking and distress in the chest, may have been the initial manifestation of an allergic condition. As this continued, secondary changes in the lungs took place, followed eventually by dilatation of the right side of the heart, failure of the left ventricle, edema of the lungs and death.

From the clinical standpoint obliterating arteritis of the pulmonary arterioles might well be divided into three stages:

1. The immediate anaphylactic stage is of short duration and is characterized by an abundance of symptomatic complaints and a minimum of objective findings. Discomfort in the chest and tachypnea are noted but no dyspnea and only moderate tachycardia.

2. The allergic stage is characterized by spasm of the pulmonary arterioles, accompanied with marked subjective symptoms; as the vascular changes lead to secondary changes in the lungs, moderate dyspnea, slight cyanosis and marked tachycardia are also present. There is evidence of localized fibrosis, pneumonitis and pleuritis. The involved lung shows diminished aeration and restricted mobility of the affected side and of the corresponding diaphragmatic excursion. There is likewise evidence of obstruction of the lesser circulation, in that there are an accentuated pulmonic second sound and a split first sound. The right

ventricle becomes enlarged, and there is electrocardiographic evidence of myocardial damage. The most valuable diagnostic aid is the finding of diminished oxygen saturation of the arterial blood.

3. The terminal stage is characterized by failure of the right ventricle, giving rise to relative tricuspid insufficiency, enlargement of the liver and eventual failure of the left ventricle, with edema of the lungs.

## CONCLUSION

There may be localized obliterating pulmonary arteritis without involvement of the other vessels, constituting a distinct clinical entity.

A case is reported in which this condition was diagnosed ante mortem and confirmed at autopsy.

Obliterating arteritis is differentiated from thrombo-angiitis obliterans in that the former is confined to the smallest arterioles without affecting the venous system.

The theory is advanced that the initial cause of the disease in our case was of an allergic nature. The condition began with anaphylactic shock, causing primary tachypnea with no dyspnea and resulting in interference with the pulmonary circulation. As the cause was not removed, there ensued secondary changes in the arterioles leading to obliterating arteritis, with consequent pathologic changes in the lungs. The right side of the heart became dilated as a result of enlargement of the right ventricle, producing anoxemia and abnormal electrocardiographic findings. Finally the left ventricle, which could not receive a sufficient amount of blood, dilated, and there followed ventricular failure and pulmonary edema.

The clinical course of circulatory failure in our case bears a striking resemblance to the circulatory failure secondary to bronchial asthma, with permanent changes in the lungs, producing cardiac failure from overtaxation of the right side of the heart.

The finding of diminished oxygen saturation of the arterial blood is of diagnostic significance. Also indicative of pulmonary arterial obstruction, particularly in young persons, are cyanosis, tachypnea, with no orthopnea, and tachycardia.

This condition may be divided into three stages: the immediate anaphylactic, the allergic and the terminal stage, with circulatory failure.

Dr. I. W. Held was of aid in an advisory capacity, Dr. Alfred Plaut reported on the pathologic specimens and Dr. Ella Fishberg carried out the detailed work on the association curves.

# RENAL INSUFFICIENCY FROM BLOOD TRANSFUSION

## II. ANATOMIC CHANGES IN MAN COMPARED WITH THOSE IN DOGS WITH EXPERIMENTAL HEMOGLOBINURIA

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The transfusion of incompatible blood into man is accompanied with or immediately followed by chills, fever, nausea and vomiting, acute pains in the muscles, dyspnea and a feeling of constriction in the chest. Signs of hemolysis in vivo may occur within a few hours. These include hemoglobinemia, hemoglobinuria and jaundice. If a relatively small amount of blood is hemolyzed, hemoglobinuria and jaundice may not be evident. Drabkin [1] has shown that only about 10 per cent of the hemoglobin that disappears from the blood stream of the dog appears in the urine. The patient may recover with nothing more serious than the loss of the transfused erythrocytes and consequent hemoglobinuria for several days. In some cases, however, the sequelae are more grave. The urinary excretion is immediately diminished, or ceases entirely, and the products of nitrogen metabolism increase rapidly in the blood. Vomiting continues, and generalized edema sometimes appears. Coma gradually supervenes, sometimes with convulsions, and the patient dies with the usual signs of uremia. Hypertension is usually absent. The picture may be complicated by subserous and subcutaneous hemorrhages. Death usually occurs from four to twelve days after the transfusion. At any time after the transfusion, spontaneous diuresis may occur, and recovery may take place. This probably happens in only a minority of the cases.

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From the Department of Internal Medicine and the Department of Pathology, the State University of Iowa College of Medicine.

1. Drabkin, D. L.; Widerman, A. H., and Landow, H.: Fate of Hemoglobin Injected into the Blood Stream, J. Biol. Chem. **109**:xxvii-xxviii (May) 1935.

A similar syndrome has been noted in blackwater fever and in hemoglobinuria due to quinine.[2]

In 1931 Bordley [3] reviewed the literature and discussed four theories which might explain the renal lesions resulting from reactions to blood transfusion: 1. The theory of mechanical blockage of the renal tubules was first proposed by Yorke and Nauss [4] and later amplified and defined by Baker and Dodds.[5] In its present form, as elaborated by the experiments of the latter authors, it attempts to account for the renal insufficiency by the precipitation of hemoglobin in the renal tubules when that pigment makes contact with urine which is acid in reaction. The hemoglobin is excreted in solution when the urine is alkaline. The operation of this mechanism was conclusively demonstrated by Baker and Dodds in rabbits. 2. The theory of anaphylaxis was derived from some observations made by Longcope and Rackemann [6] that in patients with urticaria, renal insufficiency developed coincidently. DeGowin, Osterhagen and Andersch,[7] however, have produced the syndrome in dogs with a single transfusion of canine hemoglobin. 3. The theory that renal damage is in some way a result of the hypochloremia due to vomiting was advanced on the basis of the clinical studies on high intestinal obstruction by Brown, Eusterman, Hartman and Rowntree.[8] Some of their patients died of renal insufficiency and proved to have necrosis of the tubular epithelium. Chemical studies of the blood of patients with transfusion anuria have shown that the plasma chlorides are depleted only after renal insufficiency has developed. 4. The explanation that a nephrotoxic substance is released from the hemolysis of blood seems to coincide with the acute nephrotic type of lesion seen in some of the human cases. No experimental proof has been advanced for this theory. To these four theories the independent investigations

2. Terplan, K. L., and Javert, C. T.: Fatal Hemoglobinuria with Uremia from Quinine in Early Pregnancy, J. A. M. A. **106**:529-532 (Feb. 15) 1936.

3. Bordley, J., III: Reactions Following Transfusion of Blood with Urinary Suppression and Uremia, Arch. Int. Med. **47**:288-315 (Feb.) 1931.

4. Yorke, W., and Nauss, R. W.: The Mechanism of the Production of Suppression of Urine in Blackwater Fever, Ann. Trop. Med. **5**:287-312, 1911.

5. Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules During the Excretion of Hemoglobin, Brit. J. Exper. Path. **6**:247-260 (Oct.) 1925.

6. Longcope, W. T., and Rackemann, F. M.: Renal Insufficiency with Urticaria, J. Urol. **1**:351-366 (Aug.) 1917.

7. DeGowin, E. L.; Osterhagen, H. F., and Andersch, M.: Renal Insufficiency from Blood Transfusion: I. Relation to Urinary Acidity, Arch. Int. Med. **59**: 432-444 (March) 1937.

8. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425-455 (Sept.) 1923.

of Mason and Mann,[9] in the United States, and Hesse and Filatov,[10] in Russia, have added another alternative explanation. They have shown that the intravenous injection of hemoglobin produces a diminution in the volume of the kidney by vasoconstriction. The Russian writers have stated the opinion that the renal insufficiency is on the basis of ischemia of the kidneys. The experiments of Mason and Mann have shown that the vasoconstriction is only a transitory phenomenon, and it is difficult to reconcile this theory with the anatomic lesions seen in human kidneys.

It seems that histologic studies of the kidneys of patients dying of transfusion anuria should definitely confirm or disprove the theory of pigment obstruction of the renal tubules. In reading the literature, however, one finds no consensus regarding the cause of the renal insufficiency. Practically all writers describe some necrosis of the renal epithelium and the presence of some hemoglobin pigment, but the extent of these changes varies considerably in different cases. Whereas one patient shows extensive epithelial damage and little pigment, another may show little necrosis and much precipitated hemoglobin. Because of the scarcity of cases, no one writer has had the opportunity to study more than two or three. Still fewer observers have been able to compare human tissues with those of experimental animals. As a result, some writers support the theory of mechanical obstruction, and others with an equal amount of experience but with dissimilar cases are proponents of a nephrotoxic reaction.

## MATERIAL AND METHOD

We have had the opportunity of making an examination of the tissues of five patients from our own autopsy service and those of two patients from the autopsy service of Dr. E. T. Bell, professor of patholoy at the University of Minnesota. Single specimens were lent to us by Dr. M. F. Hassett, of St. Paul; Dr. M. L. Weinstein, of Chicago, and Dr. A. M. Moody, of San Francisco. In addition, the renal sections of a woman dying of hemoglobinuria due to quinine were lent to us by Dr. K. L. Terplan, of Buffalo. The latter case was reported by Drs. Terplan and Javert.[2] Our own experiments on dogs have provided an abundance of pathologic material for comparison. The details of these experiments have already been published.[7] Dogs were fed with beef and ammonium chloride so that the urine was acid in reaction. They were then given transfusions of solution of canine hemoglobin. This resulted in death in uremia in four to ten days. This syndrome did not occur in dogs which were given transfusions when the urinary reaction was alkaline.

9. Mason, J. B., and Mann, F. C.: Effect of Hemoglobin on Volume of the Kidney, Am. J. Physiol. **98**:181-185 (Sept.) 1931.

10. Hesse, E., and Filatov, A.: Experimentelle Untersuchungen über das Wesen des hämolytischen Shocks bei der Bluttransfusion und die therapeutische Beeinflussung desselben; I. Die Nierenfunktionsstörungen im akuten Experiment, Ztschr. f. d. ges. exper. Med. **86**:211-230, 1933. Iljin, W.: Experimentelle Beobachtungen der Nierentätigkeit nach Einführung von heterogenem und autohämolysiertem Blut, Arch. f. klin. Chir. **181**:240-249, 1934.

TABLE 1.—*Summary of Anatomic Data for Dogs Dying of Causes Other Than Uremia*

| Dog No. | Urinary Reaction | Cause of Death | Number of Transfusions | Days Lived After Transfusion | Maximum Blood Urea Nitrogen, Mg. per 100 Cc. | Liver | | Kidneys | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Necrosis | Hemosiderin | Hemosiderin | Tubular Dilatation | Pigment Casts and Crystals | Tubular Necrosis | Regeneration of Epithelium | Interpretation |
| 3 | Alkaline | Killed | 14 | 8 | 11.9 | 0 | ++++ | ++++ | 0 | 0 | 0 | 0 | Normal except for hemosiderosis |
| 4 | Alkaline | Killed | 9 | 50 | 46.9 | 0 | ++++ | ++++ | 0 | 0 | 0 | 0 | Normal except for hemosiderosis |
| 7 | Acid | Speed shock | 2 | 0 | 28.0 | 0 | ++ | + | ++ | 0 | 0 | 0 | Normal except for hemosiderosis |
| 9 | Acid | Pneumonia | 2 | 1 | 47.6 | 0 | ++ | + | 0 | + | 0 | 0 | Normal except for hemosiderosis |
| 13 | Alkaline | Toxic blood | 8 | 0 | 30.1 | 0 | ++ | ++ | 0 | 0 | 0 | 0 | Normal except for hemosiderosis |
| 14 | Acid | Pneumonia | 2 | 3 | 15.0 | 0 | + | + | 0 | 0 | 0 | 0 | Normal except for hemosiderosis |
| 15 | Acid | Toxic blood | 4 | 0 | 23.1 | 0 | + | + | ++ | + | 0 | 0 | Slight pigment obstruction |
| 16 | Acid | Toxic blood | 3 | 0 | 30.8 | 0 | ++ | + | + | + | 0 | 0 | Slight pigment obstruction |
| 19 | Acid | Speed shock | 1 | 0 | 31.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Normal |

MORBID ANATOMY OF DOGS WITH HEMOGLOBINURIA

Our pathologic studies included the postmortem examination of the tissues of twenty-four dogs which had received from one to fourteen transfusions of hemolyzed erythrocytes from other dogs. The interval between transfusions was never less than one week. The average dose was 10 cc. of packed erythrocytes per kilogram of body weight. The blood was defibrinated, and the corpuscles were separated from the serum by centrifugation and were hemolyzed by the addition of distilled water in the proportion of 3 volumes of cells to 4 volumes of water. Dogs were selected which appeared healthy and whose urine was consistently free from albumin. These precautions proved to be adequate so that little evidence of chronic nephritis was observed at autopsy and no lesions were encountered which confused the anatomic picture in which we were interested.

At each transfusion the dose of solution of hemoglobin was sufficient to produce gross hemoglobinuria for two or three days. Chemical tests for hemoglobin in the urine gave positive results for approximately two more days. Casts of pigment never appeared in the urine except when there was retention of nitrogen in the blood.

*Deposition of Hemoglobin Pigment in the Tissues* (figs. 1 and 2).—With each transfusion there was a deposition of hemosiderin in the tissues. This occurred in all dogs whether or not death had occurred from renal insufficiency. The amount of hemosiderin was roughly proportional to the number of transfusions received. With relatively few transfusions, granules of pigment could be seen in the renal epithelium and in the Kupffer cells of the liver. The granules were small, and in sections stained with hematoxylin and eosin they appeared golden yellow. They gave the iron reaction with potassium ferrocyanide stains. In the kidney the cells of the proximal convoluted tubules contained large amounts of similar pigment. Occasionally some pigment could be seen in the cells of other portions of the renal tubules, even in the collecting tubules. When larger amounts of hemoglobin had been injected, hemosiderin was accumulated in the stroma near the capsule and along radial lines projecting into the cortex.

In the liver the hemosiderin was present in the Kupffer cells. When repeated injections of hemoglobin had been given, dense pigment masses were also aggregated in discrete foci of large mononuclear cells scattered throughout the hepatic substance.

The reticulo-endothelial cells of the spleen and lymph nodes also contained deposits of hemosiderin.

*Anatomic Picture in Dogs with Alkaline Urine* (figs. 1, 2 and 7 and table 1).—Dogs 3 and 4 were killed after fourteen and nine transfusions, respectively. The tissues were entirely normal except for the deposits of hemosiderin previously described. Dog 12 received a similar alkaline

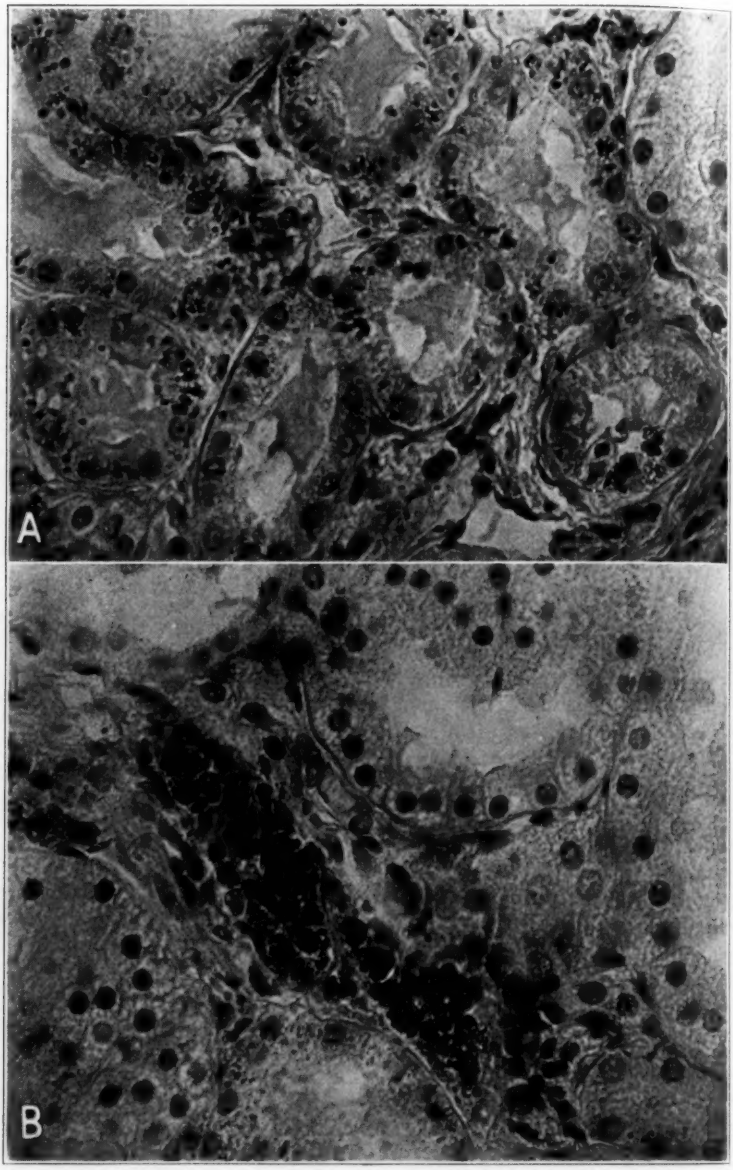


Fig. 1.—Deposition of hemosiderin. *A*, renal convoluted tubules, showing the epithelial cells containing granules of hemosiderin (photographed as black dots). Photomicrograph of tissue from dog 4 which was killed after receiving nine transfusions of hemoglobin when the urine was alkaline. *B*, an island in the renal stroma composed of masses of hemosiderin granules and large mononuclear cells (dog 4).

diet but at times refused to eat, and on those occasions the urine became acid. When a transfusion was given while the urine was alkaline, no retention of nitrogen developed; if it was given when the urine was acid, various degrees of azotemia were induced. The animal was killed when recovering from one episode of uremia, and the kidneys showed the typical nephropathic picture to be described in association with dogs with acid urine. Dog 13 was killed inadvertently with solution of

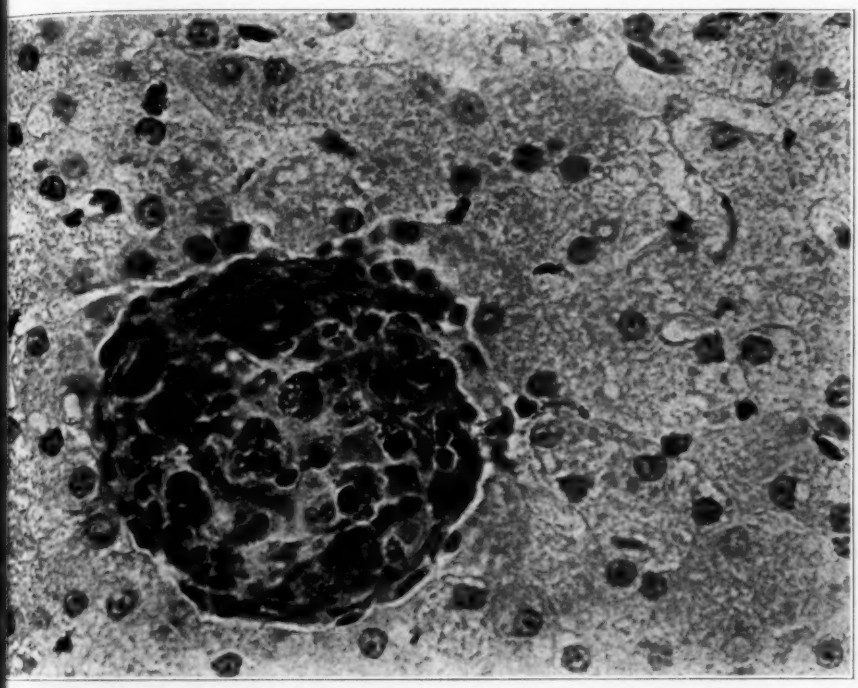

Fig. 2.—Deposition of hemosiderin. Section of liver, showing several isolated cells of Kupffer containing granules of hemosiderin and a large island of hemosiderin granules and mononuclear cells in the parenchyma (dog 4).

hemoglobin which was grossly contaminated with bacteria and which proved highly toxic for all four dogs to which it was given. The liver and kidneys, however, except for some hemosiderosis, were entirely normal.

*Anatomic Picture in Dogs with Acid Urine* (figs. 3 to 10 and table 2).—Six dogs with acid urine died from causes other than uremia. Two died of "speed shock" (dogs 7 and 19), two died of bronchopneumonia

TABLE 2.—*Summary of Anatomic Data for Dogs Dying of Uremia*

| Dog No. | Urinary Reaction | Cause of Death | Number of Transfusions | Days Lived After Transfusion | Maximum Blood Urea Nitrogen, Mg. per 100 Cc. | Liver | | Kidneys | | | | | Interpretation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Necrosis | Hemosiderin | Hemosiderin | Tubular Dilatation | Pigment Casts and Crystals | Tubular Necrosis | Regeneration of Epithelium | |
| 1 | Acid | Uremia | 4 | 10 | 119.0 | 0 | ++++ | ++++ | + | +++ | ++ | + | Pigment obstruction |
| 2 | Acid | Uremia | 2 | 9 | 217.7 | ++ | ++++ | ++++ | +++ | ++ | ++ | ++ | Pigment obstruction |
| 5 | Acid | Uremia | 3 | 8 | 217.7 | 0 | ++++ | ++++ | +++ | +++ | + | + | Pigment obstruction |
| 11 | Acid | Uremia | 2 | 4 | 350.0 | + | + | 0 | +++ | ++++ | +++ | +++ | Pigment obstruction and necrosis |
| 12 | Acid | Killed (recovering from uremia) | 10 | 9 | 133.9<br>123.0* | 0 | ++ | ++++ | +++ | ++ | + | ++ | Pigment obstruction |
| 20 | Acid | Killed (recovering from uremia) | 1 | 5 | 119.0<br>95.6* | 0 | + | + | +++ | ++ | + | ++ | Pigment obstruction |
| 21 | Acid | Uremia | 1 | 4 | 266.7 | 0 | +++ | + | + | +++ | ++++ | ++ | Pigment obstruction and necrosis |
| 23 | Acid | Uremia | 1 | 7 | 324.1 | 0 | + | + | + | + | ++ | 0 | Tubular necrosis |
| 24 | Acid | Uremia | 1 | 7 | 362.6 | 0 | +++ | + | ++ | ++++ | ++ | ++++ | Pigment obstruction |

* The value at the time the dog was killed.

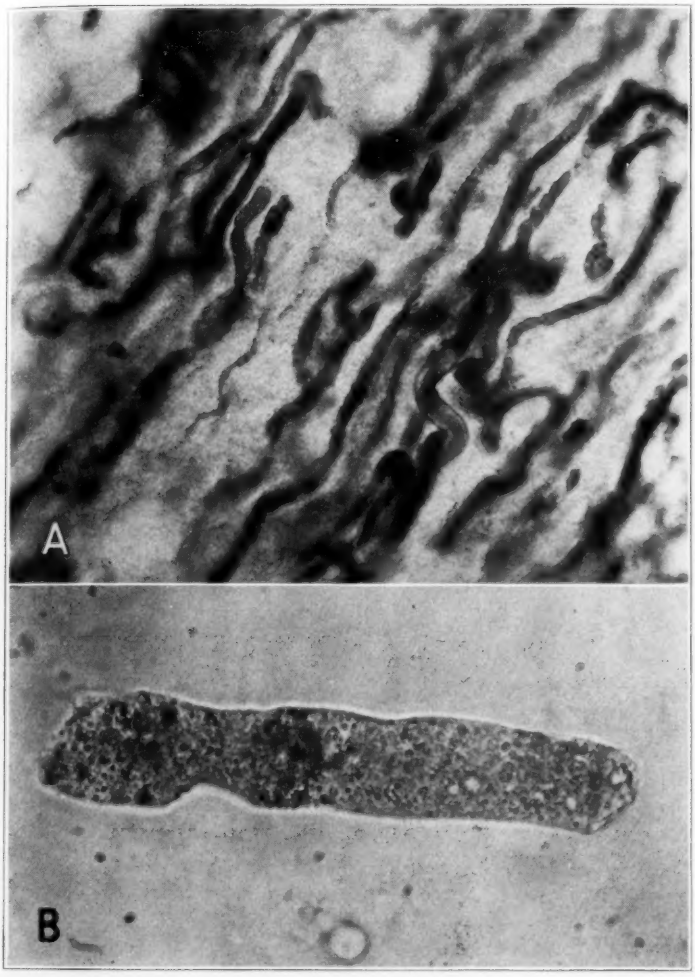


Fig. 3.—Tubular obstruction. *A*, unfixed and unstained section of kidney, photographed one hour post mortem, showing tubular lumens outlined by brown pigment casts. Several loops of Henle are shown. Section from the kidney of dog 21, which died of uremia four days after a single transfusion received when the urine was acid. *B*, a single pigment cast teased from the preparation pictured in *A*. The cast was brown and opaque and when viewed through the microscope seemed composed of small masses of pigment molded together.

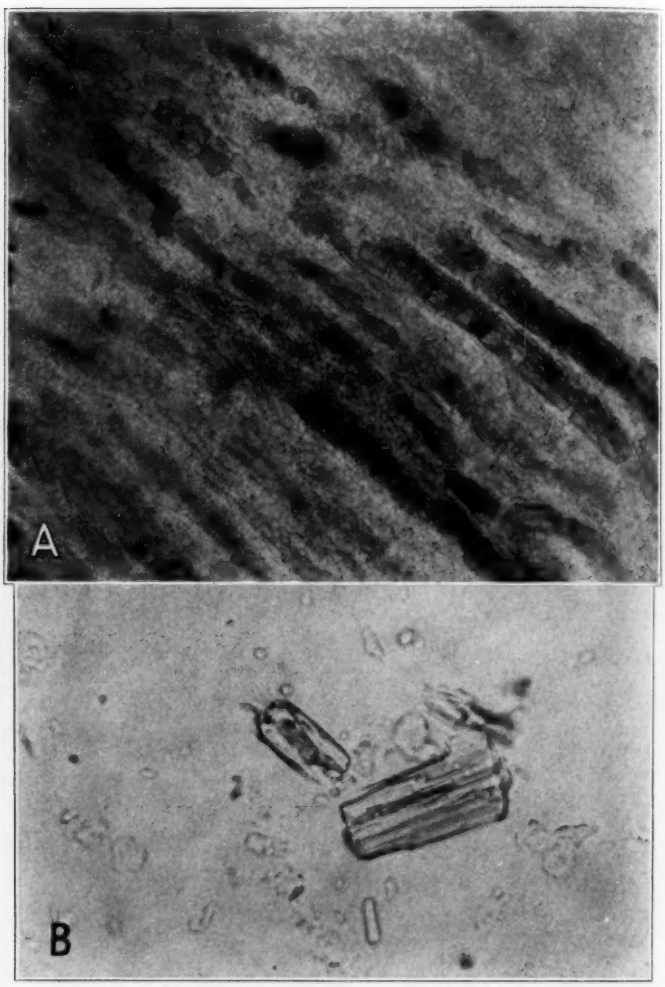


Fig. 4.—Tubular obstruction. *A*, tubular lumens filled with brown crystals of pigment. This is in the medullary region of the same preparation depicted in figure 3 *A*. *B*, two brown crystals teased from the preparation pictured in *A*. The form of the crystals resembles that of canine hemoglobin.

(dogs 9 and 14) and two died because the solution of hemoglobin was contaminated (dogs 15 and 16). In none of these were there significant lesions of the kidneys or liver except for the hemosiderosis common to all dogs receiving solution of hemoglobin. In dogs 15 and 16 there were, however, a few pigment casts, indicating an early stage of obstruction. This group served as controls to show that the diet of beef and ammonium chloride produced no renal damage.

Fig. 5.—Tubular obstruction. Pigment casts were formed in the region of the corticomedullary junction and followed the cortical rays toward the periphery. Peripherally from this zone of casts, the lumens were dilated. Low magnification of a fixed and stained sagittal section from the kidney of dog 2, which died in uremia nine days after receiving a transfusion when the urine was acid.

Seven dogs (dogs 1, 2, 5, 11, 21, 23 and 24) died in uremia and two (dogs 12 and 20) were killed when recovering from episodes of azotemia. The livers of dogs 2 and 11 contained some necrosis about the central veins of the lobules. In all other dogs of both groups the livers were essentially normal except for the hemosiderosis previously described.

The kidneys of the dogs dying of renal insufficiency showed striking pictures. They were slightly increased in size. The capsules were not adherent. Fresh sections revealed a dark reddish brown zone marking the corticomedullary junction, with radial projections of the same color extending into the cortex. When thin slices of fresh kidney were examined with a dissecting microscope by transmitted light, Henle's loops, the recurring limbs and the collecting tubules were seen to

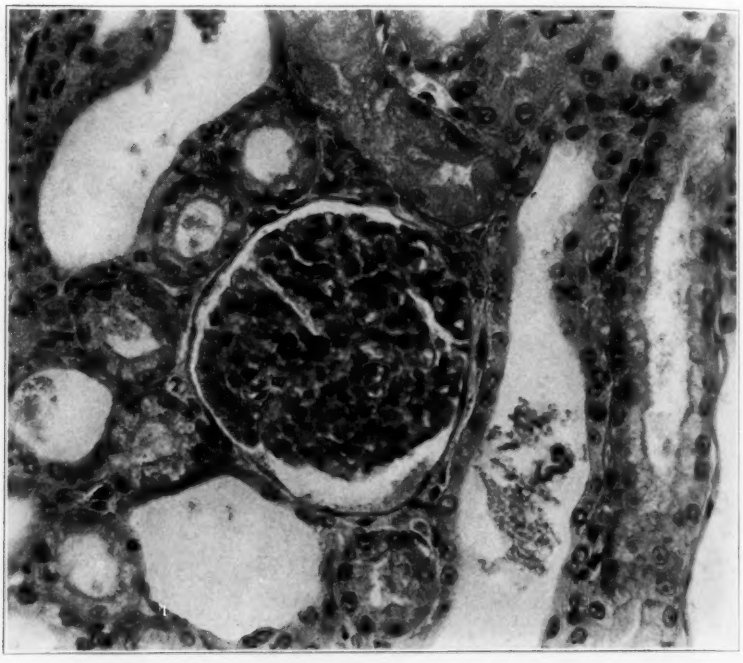

Fig. 6.—Tubular obstruction. This illustration depicts a normal glomerulus and moderate dilatation of the lumens of the convoluted tubules (dog 2).

be filled with a dark brown substance. In some areas brown crystals could clearly be seen in the lumens of the tubules. The crystals belonged to the monoclinic system. With teasing needles some of the casts and crystals were dislodged and photographed. This proved conclusively that the brown of the pigment casts was natural and that the crystals were not artefacts produced by staining and fixation. It has so far proved impracticable to separate enough material for spectroscopic and chemical analysis.

The kidneys were fixed in Zenker's solution and stained with hematoxylin and eosin. When appropriate sections were studied under low magnification, a broad zone could be seen in the region of the corticomedullary junction. This area was remarkable because of the large numbers of pigment casts and crystals in the tubular lumens. The cortical rays also were made prominent because they were filled with the same substances.

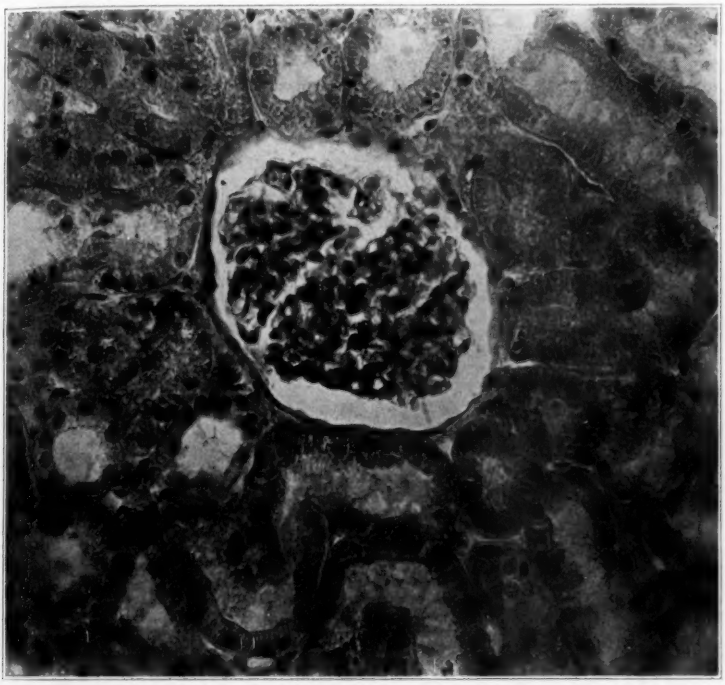

Fig. 7.—Normal dog kidney (to be compared with figure 6). A normal glomerulus with undilated tubules. The tubular epithelium contains granules of hemosiderin. Photomicrograph of section of tissue from dog 3, which was killed after fourteen transfusions, given when the urine was alkaline.

With higher magnification the glomeruli appeared normal. The crystals and casts occurred chiefly in the lumens of Henle's loops and of the recurring limbs and to a lesser extent in the collecting tubules. Proximal to these obstructions, the lumens of the descending limbs and the spaces of Bowman were dilated. The pigment masses and crystals appeared greenish brown. This was in contrast to the brownishness seen in the fresh, unfixed and unstained preparations. The green tint was probably caused by the action of the fixative on the pigment. The

greenish brown was also in contrast to the golden yellow of the hemosiderin contained in the epithelial cells. This suggests the inference that the pigment casts and crystals are not hemosiderin. This is supported by the fact that they did not give the prussian blue reaction. A few lumens were filled with polymorphonuclear leukocytes. Patchy areas of stroma were infiltrated with leukocytes. Special stains, however, never revealed the presence of bacteria.

Adjacent to the pigment casts and crystals there was some degeneration of epithelium. This was not marked. However, occasional necrotic

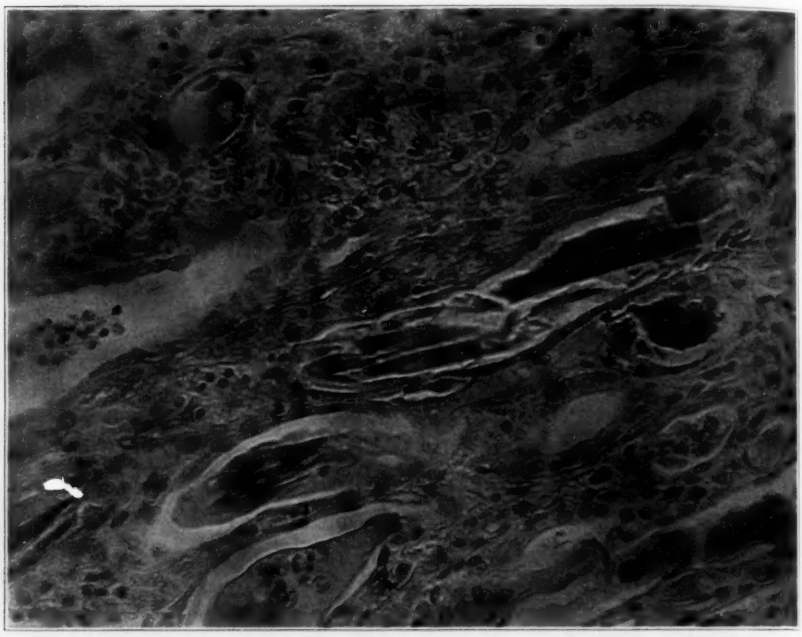

Fig. 8.—Tubular obstruction. Tubular lumens in the region of Henle's loops were filled with greenish brown crystals of pigment, casts of amorphous pigment and some leukocytes. This section is from the same kidney as the section pictured in figure 5.

cells occurred in tubules which did not contain casts, and careful search usually revealed mitotic figures as evidence of regeneration. In some places tubules were lined with low cuboidal epithelium which could be interpreted either as regenerating epithelium or as residua after sloughing of portions of the cells.

In most of the kidneys studied the amount of necrosis was minimal. The essential lesion appeared to be simple mechanical blockage of the

tubules with pigment casts and crystals. The evidence of epithelial injury was marked in one dog (dog 21). In this animal, in addition to extensive obstruction, there was an extreme degree of necrosis of the cells of the convoluted tubules and deposition of calcium salts in some of the necrotic cellular débris.

From the histologic changes observed it was evident that two distinct and apparently separate pathologic processes were involved. The most common and striking one was that of tubular obstruction by pigment

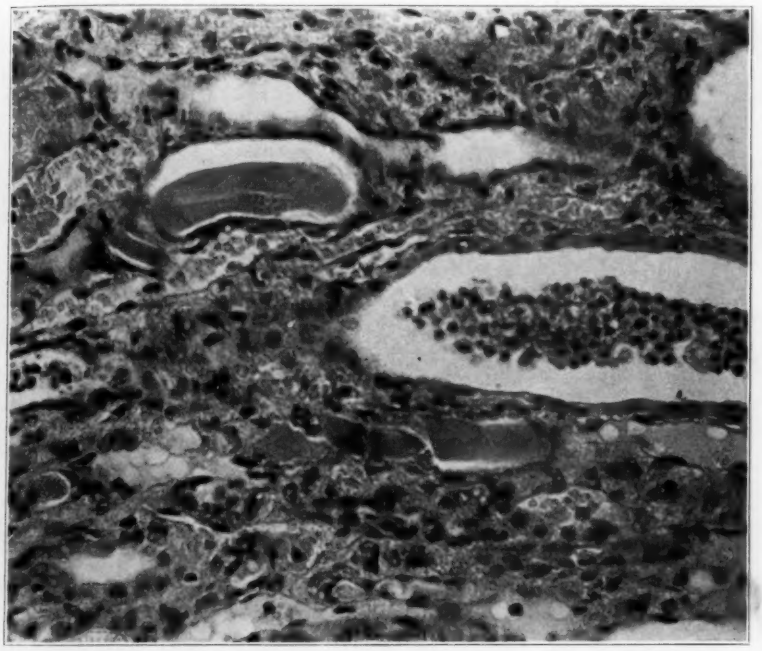

Fig. 9.—Tubular obstruction. Collecting tubules filled with leukocytes and pink-staining albuminous material. This section is from the same kidney as the section depicted in figure 5.

precipitated in the region of Henle's loops. The other was a destructive process involving particularly the epithelium of the convoluted tubules. The kidneys of dogs 1, 2, 5, 12, 20 and 24 showed the obstructive process in marked predominance. Dogs 21 and 11 showed a combination of extensive necrosis and marked obstruction with pigment. There was no significant obstruction in the kidneys of dog 23, and the amount of necrosis was not as extensive as that in dogs 21 and 11. No

correlation could be made between the occurrence of the type of lesion and any other factor. Neither the period of survival after transfusion nor the amount of retention of nitrogen seemed to have a direct relation. Many mitotic figures were seen in kidneys of animals which lived only four days after transfusion.

The most striking demonstration of the two types of renal lesions was obtained by study of dogs 23 and 24. These two animals both had acid urine, and the transfusions were given within the same hour with the same lot of solution of hemoglobin. The clinical courses were

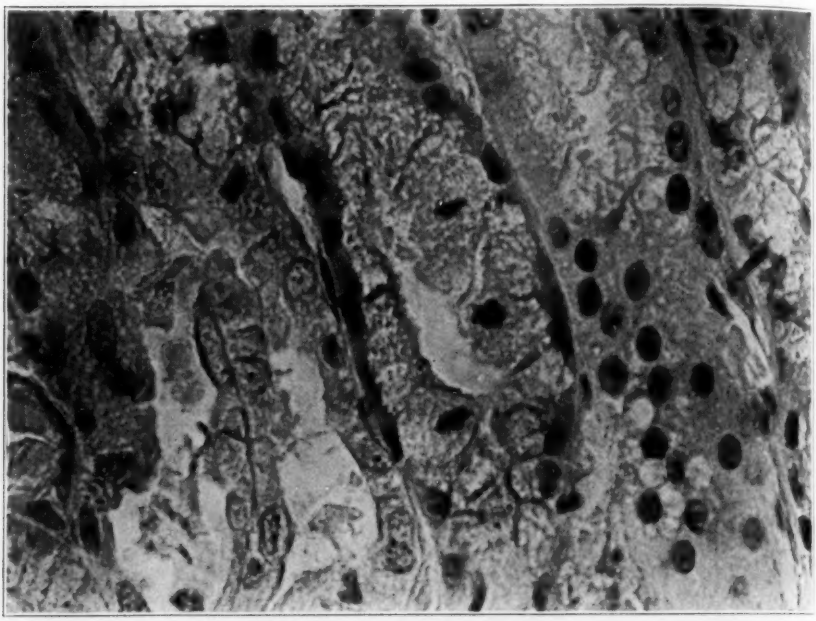

Fig. 10.—Tubular regeneration. Three mitotic figures are shown in the cross-section of a single convoluted tubule. In most kidneys, however, evidence of regeneration was not as common as is depicted here. Photomicrograph of a section of tissue from dog 24, which died in uremia seven days after a single transfusion received when the urine was acid.

unusually similar, both animals dying in coma seven days after the transfusion, with urea nitrogen values of 324.1 and 362.6 mg. per hundred cubic centimeters of blood, respectively. The kidneys of dog 23 showed moderate necrosis and practically no obstruction with pigment, but the kidneys of dog 24 contained extensive obstructive lesions and a minimal amount of necrosis.

MORBID ANATOMIC PICTURE IN PATIENTS WITH POST-TRANSFUSION UREMIA (TABLE 3)

Studies were made of the kidneys of eight patients who died of renal insufficiency following blood transfusion and of one patient who died of uremia following hemolysis from quinine. Five patients with transfusion reactions were from our own autopsy service, and microscopic sections of the remaining four were lent to us by others. The kidneys of our patients were somewhat enlarged and congested. On section, brownish radial streaks could often be made out in the medulla. Microscopically, the anatomic basis for the renal insufficiency was not evident in the majority of the cases studied. Perhaps the most constant abnormality was edema of the interstitial tissues. A variable number of brown pigment casts were observed in the tubules, especially in Henle's loops and in the collecting tubules. Although in many of the cases there were not enough pigment casts to interfere seriously with renal function, nevertheless in our experience the presence of these casts has been the most diagnostic anatomic feature of renal insufficiency following transfusion. There was some degeneration of the epithelium adjacent to the casts, and necrotic cells were occasionally unassociated with casts. This was not striking in any of the cases studied. In two cases considerable hemosiderin was deposited in the tubular epithelium. Dilatation of convoluted tubules was usually present and marked. Many of the tubules were lined with low cuboidal epithelium, suggesting either a previous sloughing of the superficial portion or regeneration of cells. Mitotic figures, however, were found only with difficulty. Occasional tubules contained polymorphonuclear leukocytes. The glomerular tufts appeared essentially normal.

In two of the cases the kidneys were so badly damaged by the primary renal lesion that the lesions incident to the transfusion reaction were overshadowed except for the presence of scattered pigment casts.

Qualitatively, the characteristics were essentially the same as those observed in the dogs, except that in the human kidneys there were frequent hemorrhages into the tubular lumens which were not present in the dogs. Neither the accumulation of pigment débris in the tubular lumens nor the necrosis of epithelium was as marked as in the dog kidneys. A satisfactory anatomic basis for the renal insufficiency was often lacking in the human material.

## COMMENT

In our experiments on hemoglobinuria in dogs the chemical evidence and the clinical course indicated fairly clearly that death was the result of renal insufficiency. No significant anatomic changes outside the kidneys were noted except in two dogs which showed some necrosis of

TABLE 3.—*Summary of Anatomic Data for Human Beings Quantitatively Compared with Those for Dogs* *

| Cases | Diagnoses | Sex | Age, Years | Days Lived After Transfusion | Chemical Evidence of Uremia in Blood | Liver | | Kidneys | | | | | | | Interpretation of Anatomic Changes in Terms of Renal Function |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Necrosis | Hemosiderosis | Hemosiderosis | Tubular Dilatation | Pigment Casts | Pigment Crystals | Tubular Necrosis | Mitoses in Epithelium | Interstitial Edema | |
| Our case 1 W. B. | Duodenal ulcer | M | 65 | 10 | Urea nitrogen, 183.4 mg.; creatinine, 17.6 mg. | + | 0 | 0 | + | + | 0 | p | p | + | Toxic injury; changes not extensive |
| 2 A. Z. | Pernicious anemia | M | 57 | 10 | Urea nitrogen, 155.4 mg.; creatinine, 12.3 mg. | 0 | + | ± | ± | ± | 0 | p | 0 | p | Toxic injury; changes not extensive |
| 3 A. P. | Pyelonephritis | M | 57 | 3 | Urea nitrogen, 105.7 mg.; creatinine, 11.4 mg. | 0 | 0 | 0 | ++ | p | 0 | ? | 0 | 0 | Damage complicated by prior nephritis |
| 4 E. S. | Chronic nephritis | F | 50 | 16 | Urea nitrogen, 130.2 mg.; creatinine, 10.3 mg. | .. | .. | 0 | + | ± | 0 | ? | 0 | 0 | Damage complicated by prior nephritis |
| 5 D. B. | Craniotomy | M | 28 | 3 | Urea nitrogen, 119 mg.; creatinine, 8.7 mg. | + | 0 | 0 | p | + | 0 | 0 | 0 | p | Toxic injury; changes not extensive |
| Weinstein's case | Prostatic resection | M | 60 | 6 | Urea nitrogen, 140 mg.; creatinine, 10.4 mg. | .. | .. | ± | ± | ++ | 0 | 0 | 0 | 0 | Pigment obstruction a factor in uremia |
| Terplan's case | Quinine hemoglobinuria | F | 41 | .. | Urea nitrogen, 344 mg.; creatinine, 16.2 mg. | 0 | + | p | ± | +++ | 0 | p | 0 | ± | Pigment obstruction a factor in uremia |
| Hassett's case | Abortion | F | 26 | 12 | Urea nitrogen, 207 mg. | + | + | 0 | + | + | 0 | p | 0 | ± | Toxic injury; changes not extensive |
| Moody's case | Aleukemic leukemia | M | 37 | 25 | ..... | 0 | + | + | ± | + | 0 | p | 0 | p | Toxic injury; changes not extensive |

* An attempt has been made to indicate the occurrence of the anatomic lesions quantitatively by direct comparison with the data for dog kidneys in tables 1 and 2 using the same scale. ± indicates less than +; p, present but less than ±; ?, interpretation impossible because of prior lesions.

the central zones of the hepatic lobules. The kidneys of six dogs (dogs 1, 2, 5, 12, 20 and 24) gave satisfactory evidence of extensive obstruction with pigment of the tubules in the region of the loops of Henle; there was a minimal amount of tubular necrosis. These six kidneys, then, presented an anatomic picture of relatively pure obstruction with pigment. Physiologic disturbances, in addition to obstruction, cannot, of course, be excluded on an anatomic basis. From the anatomic criteria, the hypothesis of Baker and Dodds [6] can explain these lesions. These writers have demonstrated that hemoglobin forms a precipitate in solutions comparable to urine with an acid reaction. Richards and Walker [11] have stated that the glomerular filtrate in the amphibian tubule first becomes acid in the region of Henle's loop. This location for the dog's kidney can be only inferred at present, but the assumption of a similar situation will explain the lesion which we have described. The hypothesis will also explain why dogs which were given transfusions when the urine was alkaline did not show renal lesions.

In three other dogs (dogs 11, 21 and 23) there was evidence of a severe grade of tubular necrosis as well as some obstruction with pigment. Of these, only dog 11 had hepatic necrosis. In dog 23 the tubular necrosis overshadowed the obstruction so completely that we were forced to the conclusion that the latter process could not have produced serious interference with renal function.

From our anatomic studies of dogs we conclude that the mechanism of obstruction of renal tubules with hemoglobin pigment may be the chief cause of renal insufficiency but that there is another, probably independent, process operating which causes tubular necrosis and which may be severe enough to cause death.

The deposition of hemosiderin in the tubular epithelium has impressed some authors [12] as being a possible cause of impaired function. In our studies of dogs this seems to be a part of the physiologic process which occurs whenever hemoglobin is free in the blood stream. The pigment is taken up not only by the tubular epithelium of the kidney but also by the Kupffer cells in the liver and by the reticulo-endothelium of the spleen and lymph nodes. When repeated injections are given, hemosiderin is aggregated in masses of mononuclear cells in the parenchyma of the liver and the interstitial tissue of the kidney. It does not appear, however, that this process leads to impairment of function. Renal insufficiency occurred in some dogs with only minor grades of hemosiderosis.

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11. Richards, A. N., and Walker, A. M.: Urine Formation in the Amphibian Kidney, Am. J. M. Sc. **190**:727-746 (Dec.) 1935.

12. Lichty, J. A.; Havill, W. H., and Whipple, G. H.: Renal Thresholds for Hemoglobin in Dogs, J. Exper. Med. **55**:603-615 (April) 1932. Bordley.[8]

TABLE 4.—*Summary of Anatomic Data for Cases Described by Various Authors* *

| Authors | Case No. | Diagnosis | Sex, Age, Yr. | Days Lived After Transfusion | Chemical Evidence in Blood of Uremia | Liver | | Kidneys | | | | | | | Authors' Interpretation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Necrosis | Hemosiderosis | Hemosiderosis | Tubular Dilatation | Pigment Casts | Pigment Crystals | Tubular Necrosis | Regenerating Epithelium | Interstitial Edema | |
| Bordley[3] | 3 | Pernicious anemia | M 39 | 10 | Nonprotein nitrogen, 186 mg.; creatinine, 10.1 mg. | + | + | + | + | + | 0 | + | + | + | |
| Goldring and Graef[13b] | 1 | Diabetic gangrene | M 55 | 7 | Nonprotein nitrogen, 102 mg. | + | + | + | + | + | + | + | + | + | Acute nephrosis |
| Goldring and Graef[13b] | 4 | Puerperal sepsis | F 24 | 19 | Nonprotein nitrogen, 245 to 180 mg. | 0 | 0 | — | — | + | 0 | + | 0 | + | Acute nephrosis |
| Baker and Dodds[5] | 1 | Gastric ulcer | F 38 | 4 | Nonprotein nitrogen, 206 mg.; creatinine, 6 mg. | 0 | 0 | — | + | + | 0 | 0 | 0 | 0 | Pigment obstruction |
| Baker and Dodds[5] | 2 | Cholelithiasis with jaundice | F 54 | 17 | Nonprotein nitrogen, 800 mg.; urea, 920 mg.; creatinine, 26 mg. | 0 | 0 | — | 0 | 0 | 0 | + | 0 | 0 | Pigment obstruction plus some other factor |
| Witts[13d] | .. | Postpartum anemia | F 29 | 11 | Urea, 354 mg. | — | — | + | + | + | 0 | + | + | + | "Hemoglobin infarction of the kidneys" |
| Shera[13e] | .. | Ruptured ectopic pregnancy | F 36 | 8 | Urea, 174 mg. (3d day) | 0 | 0 | — | + | + | 0 | + | 0 | 0 | Pigment obstruction |
| Payne[13f] | .. | Acute hemolytic anemia | M 20 | 3 | Urea, 157 mg. | 0 | 0 | — | + | + | 0 | 0 | 0 | 0 | "Hemoglobin infarction of the kidneys" |
| Lemke[13g] | 1 | Ruptured tubal pregnancy | F 32 | 6 | ..... | + | — | — | 0 | + | 0 | 0 | 0 | — | |
| Liège and Herr[13h] | 1 | Posthemorrhagic anemia | M 9 | 9 | Urea, 400 mg. | .. | .. | .. | .. | .. | .. | .. | .. | .. | "Blockage of the tubules" |
| Liège and Herr[13h] | 2 | Acute mastoiditis | F 6 | 2 | Urea, 203.5 mg. | .. | .. | .. | .. | .. | .. | .. | .. | .. | "Blockage of the tubules" |
| Lindau[13i] | 1 | Gastric hemorrhage | M 35 | 5 | "Rest nitrogen," 234 mg. | + | — | + | 0 | + | — | + | — | — | |
| Lindau[13i] | 2 | Cholelithiasis | F 28 | 9 | "Rest nitrogen," 150 mg. | — | — | + | 0 | + | — | + | — | — | |
| Lindau[13i] | 3 | Hypernephroma | M 64 | 1½ | ..... | + | 0 | — | — | — | — | + | — | — | |
| Terplan and Javert[2] | .. | Quinine hemoglobinuria and pregnancy | F 41 | Not known | Urea nitrogen, 344 mg.; creatinine, 16.2 mg. | 0 | + | + | + | + | 0 | + | 0 | — | "Distention of tubular system by masses of hemoglobin" |

* + indicates described or implied as present; 0, described or implied as not present; —, not mentioned.

We have incorporated in table 4 the principal anatomic features described by several authors [13] in isolated cases of human beings who died as a result of renal insufficiency following reactions due to blood transfusion or, in one case, following quinine hemoglobinuria. No attempt has been made to record the various lesions quantitatively, as this is manifestly impossible without studying the tissues at first hand with reference to a large series of cases. The tabulation illustrates three points: first, that most of the kidneys described resembled each other qualitatively as to the types of lesions present; second, that the quantitative relation of the various lesions must have varied considerably, as inferred from the author's final anatomic diagnosis, and, third, that the anatomic study of from one to three cases does not constitute a safe basis for generalization as to the etiology of the condition.

With separate anatomic pictures of obstruction with pigment and of a necrosing process available in our experimental material for comparison, the histologic studies of the kidneys of nine human beings who died of renal insufficiency after hemolysis has tended to clarify some of the questions relating to etiology. In all the patients there was evidence that the precipitation of hemoglobin pigment in the tubular lumens had occurred to a slight degree at least. But in most of the cases not enough tubules were obstructed to produce any important diminution in renal function. Two of the patients, however, had enough tubules obstructed to have been a possible factor in producing death. Nevertheless, the presence of pigment casts and of hemosiderosis is an important criterion in making the anatomic diagnosis of transfusion nephropathy. The predominant lesions were more often degenerative changes in the tubules and interstitial edema. In many of the cases the anatomic changes were slight and did not appear adequate to explain the renal insufficiency.

Another point to be kept in mind in comparing the human and dog kidneys was that the dose of hemoglobin administered to the dogs was probably at least twice as much as that administered to most of the patients on the basis of body weight. It should also be remembered

13. (*a*) Bordley.[3] (*b*) Goldring, W., and Graef, I.: Nephrosis with Uremia Following Transfusion with Incompatible Blood: Report of Seven Cases with Three Deaths, Arch. Int. Med. **58**:825-845 (Nov.) 1936. (*c*) Baker and Dodds.[5] (*d*) Witts, L. J.: A Note on Blood Transfusion, with an Account of a Fatal Reaction, Lancet **1**:1297-1299 (June 22) 1929. (*e*) Shera, G.: Fatal Suppression of Urine Caused by Latent Hemagglutinins, Brit. M. J. **1**:754-755 (May 5) 1928. (*f*) Payne, R. V.: Acute Hemolytic Anemia: Death After Transfusion, Guy's Hosp. Rep. **84**:65-71 (Jan.) 1934. (*g*) Lemke, R.: Pathologisch-anatomische Befunde bei Todesfällen nach Bluttransfusionen, Virchows Arch. f. path. Anat. **257**:415-429, 1925. (*h*) Liège, R., and Herr, A.: Les néphropathies graves post-transfusionelles, Ann. de méd. **34**:398-420, 1933. (*i*) Lindau, A.: Reaktionen nach Bluttransfusion: Eine ätiologische und pathologisch-anatomische Studie, Acta path. et microbiol. Scandinav. **5**:382-427, 1928. (*j*) Terplan and Javert.[2]

that there are some chemical differences between human and canine hemoglobin which might account for some of the discrepancies noted. It should be pointed out that in the kidneys of dogs 12 and 20 we had illustrations of the amount of obstruction with pigment which was less than the minimum amount necessary to produce death, as these dogs were killed when they were recovering from renal insufficiency.

## CONCLUSIONS

The transfusion of canine hemoglobin into dogs when the urine is acid results in death from renal insufficiency. This does not occur when the urine is alkaline at the time of the transfusion.

The anatomic picture of obstruction of the renal tubules by hemoglobin pigment sufficient to be the chief cause of the renal insufficiency is observed in most dogs under the experimental conditions outlined. A nephrotoxic process often operates and may cause renal insufficiency independently.

The deposition of hemoglobin pigment as hemosiderin in the renal tubules and in the reticulo-endothelial system apparently does not contribute to the development of renal insufficiency.

An anatomic study of the kidneys of nine human beings who died of renal insufficiency after hemolysis revealed the two independent mechanisms seen in dogs, the obstruction with pigment and the necrosing factor.

In occasional human beings the precipitation of hemoglobin pigment in the tubules is extensive and may be a cause of renal insufficiency. This complication could probably be prevented by alkalinizing the urine prior to the transfusion.

The renal insufficiency after hemolysis in the majority of human beings is probably caused by some nephrotoxic substance which causes degeneration of tubular epithelium and interstitial edema.

Dr. E. T. Bell, Professor of Pathology at the University of Minnesota, examined the tissue sections and offered valuable suggestions. Drs. M. F. Hassett of St. Paul, M. L. Weinstein of Chicago, K. L. Terplan of Buffalo and A. M. Moody of San Francisco furnished material from their patients.

# ASSOCIATION OF HYPERTHYROIDISM WITH PULMONARY TUBERCULOSIS

## A REVIEW OF THE LITERATURE AND REPORT OF TWENTY-THREE CASES

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The relation of the thyroid gland to tuberculosis has received much attention in the literature since about the middle of the last century. Clinical, experimental and pathologic observations have produced a diversity of opinions concerning this relation. It is our purpose to review briefly the more important views expressed in the literature and to present clinical observations on the progress of 23 patients with coexistent hyperthyroidism and pulmonary tuberculosis.

### REVIEW OF THE LITERATURE

Earlier writers (Virchow, Rokitansky and Hamburger [1]) believed an antagonism exists between tuberculosis and the thyroid gland and that the latter is immune to invasion. Infections of various types may produce diffuse temporary swelling of the thyroid and congestion or colloid goiter. This seems to be particularly true in cases of tuberculosis, in which parenchymatous or colloid goiter is relatively common.[2] Such a goiter may recede as the tuberculosis heals, but if the tuberculosis progresses there may develop in the later stages a diffuse sclerosis of the thyroid gland and in some instances, late in tuberculosis, evidence of thyroid insufficiency. In some instances diffuse sclerosis of the endocrine system has been associated with tuberculosis; in such cases it is possible that changes in the thyroid gland may have been due in part to lesions in other endocrine organs (i. e., the anterior lobe of the pituitary gland [3]). The clinical picture of mild hyperthyroidism is fre-

From the Sections on endocrine and thoracic disorders of the Medical Clinic, the Hospital of the University of Pennsylvania.

1. Virchow, Rokitansky and Hamburger, cited by Epstein.[4b]

2. Brown, P. K.: Hyperthyroidism and Tuberculosis, Tr. Am. Climat. & Clin. A. **37**:37, 1921.

3. Jedlička, V.: Relation of the Thyroid Gland to Tuberculosis, Časop. lék. česk. **75**:1521, 1936.

quently seen in cases of early tuberculosis and may confuse the diagnosis. The earlier belief that the association of tuberculosis and frank hyperthyroidism is a rarity [4] has been disproved by numerous later reports, but it seems to be true that active pulmonary tuberculosis and frank thyrotoxicosis are not commonly encountered in the same patient. Jedlička [3] has recently written an extensive review of the entire subject of the relation of the thyroid gland to tuberculosis.

*Experimental Studies.*—The protective action of the thyroid gland against tuberculosis has been studied experimentally, with conflicting results. Steinback,[5] Suzuki and Hanaoka,[6] Ishimaru [7] and others [8] have produced evidence suggesting that the presence of the thyroid gland or the administration of thyroid substance assists body defense against tuberculosis in the experimental animal. Schedtler,[9] however, found attenuation of tuberculosis in guinea pigs and rabbits after thyroid ablation, and Galli [10] found that thyroidectomized guinea pigs survived bovine tuberculosis longer than did controls. Gloyne's [11] work led him to express the belief that there is little reason to attribute a direct antitoxic action to the thyroid gland in tuberculosis.

Evidence has been found of hypertrophy [12] and hyperfunction [13] of the thyroid gland in experimental tuberculosis. Ishimaru [7] found in

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4. (*a*) West, Samuel: Thirty-Eight Cases of Exophthalmic Goitre, with Remarks, Tr. Ophth. Soc. U. Kingdom **6**:76, 1886. (*b*) Epstein, D: Tuberculose und endokrines System, Ztschr. f. Tuberk. **72**:383, 1935.

5. Steinback, M. M.: Experimental Tuberculosis in the Albino Rat: The Comparative Effects of Avitaminosis, Suprarenalectomy and Thyroid-Parathyroidectomy in Experimental Tuberculosis, Am. Rev. Tuberc. **26**:52, 1932.

6. Suzuki, K., and Hanaoka, M.: Studies on the Relation Between the Function of Internal Secretion and Tuberculous Infection: The Tuberculous Infection in the Case of Abnormality of Function of Hypophysis and Thyroid Gland, Tr. Soc. path. jap. **24**:415, 1934.

7. Ishimaru, Y.: Effect of Tuberculous Infection on the Tissues of the Thyroid and Thymus Glands, Kekkaku **13**:7 (March 25) 1935.

8. Marbé, S.: Les opsonines dans les états thyroïdiens: I. Les opsonines des animaux hyperthyroïdes, Compt. rend. Soc. de biol. **64**:1058, 1908. Stepanoff: Le corps thyroïde et les defenses naturelles de l'organisme, ibid. **66**:296, 1909. Bernard, Suzanne: Glande thyroïde et tuberculose: Influence de la thyroïdectomie sur l'évolution de la tuberculose experimentelle chez le lapin, Thesis, Paris, no. 55, 1921.

9. Schedtler, D.: Tuberkuloseablauf und Schilddrüsenfunktion, Ztschr. f. Tuberk. **70**:314, 1934.

10. Galli, R.: Tiroidectomia e decorso delle infezione: Studio morfologico delle reazioni cellulari negli animali stiroidati, Arch. ital. di chir. **41**:571, 1935.

11. Gloyne, S. R.: Experimental Tuberculosis, J. Path. & Bact. **28**:451, 1925.

12. Webb, G. B.: Immunity in Tuberculosis, J. Lab. & Clin. Med. **1**:414, 1916.

13. Hashimoto, T.: Study of Function of Thyroid Glands of Tuberculous Rabbits, J. Orient. Med. **25**:81, 1936.

guinea pigs that as the infection progressed the picture of partial hyperfunction (colloid goiter) appeared and was followed in the late stages by atrophic and degenerative changes. He also found that thyroidectomized animals infected with tuberculosis showed more marked regressive changes in the thymus and adrenal glands than did nonthyroidectomized controls. Conversely, thymectomized animals showed degenerative changes in the thyroid gland.

Frommel, Herschberg and Trottet [14] found that tuberculin hastened the metamorphosis of tadpoles somewhat but did not affect the growth or epiphysial development of young rabbits and guinea pigs. They also found that a single injection of tuberculin often caused tachycardia and thyroid congestion in guinea pigs; no response occurred after thyroid ablation.

*Iodine Content of the Thyroid Gland in Tuberculosis.*—Labbé, Vitry and Giraud [15] found a wide variation in the iodine content of the thyroid glands of 24 persons who had died of tuberculosis. This did not seem to be influenced by iodine therapy. In general, the iodine content was greater in cases of rapidly progressive than in cases of more chronic tuberculosis, leading the authors to postulate a condition of thyroid exhaustion in the latter. Piazza [16] found the iodine content of the thyroid glands of persons who had died of tuberculosis to be greater in relation to the total weight of the gland than that of the thyroid glands of persons dying of other causes.

*Basal Metabolism in Pulmonary Tuberculosis.*—This has been extensively studied, again with conflicting conclusions. Raimondi and Scartascini [17] concluded that the basal metabolic rate tends to rise with the progress of tuberculosis and to fall as healing occurs. They found a sharp drop in the metabolic rate after pneumothorax. (In this connection the findings of Abbott and his associates [18] are interesting. They reported a "reversion" of the thyroid gland to the colloid state in 31 per cent of puppies and 57 per cent of kittens after pneumothorax and oleothorax but no changes in the thyroid gland in adult dogs and cats

14. Frommel, E.; Herschberg, A. D., and Trottet, A.: Tuberculine et thyroïde: Étude expérimentale—déductions thérapeutique, Rev. de la tuberc. **11**:399, 1935.

15. Labbé, H.; Vitry, G., and Giraud, G.: Dosage de l'iode contenu dans les corps thyroïdes des tuberculeux, Compt. rend. Soc. de biol. **65**:371, 1908.

16. Piazza, R.: Il contenuto in iode della tiroide nei tubercolotici, Riforma med. **49**:325, 1933.

17. Raimondi, A. A., and Scartascini, R.: El metabolismo basal en la evolución de la tuberculosis pulmonar, Prensa méd. argent. **22**:21 (Jan. 2) 1935.

18. Abbott, A. C.; Goodwin, A. M.; Meltzer, S., and Stephenson, E.: Effect of Pneumothorax and Oleothorax on the Histologic Structure of the Thyroid Gland, Arch. Surg. **30**:667 (April) 1935.

after such procedures.) Cordier [19] stated the opinion that sudden elevation of the basal metabolic rate (fever being excluded as a cause) is a bad prognostic sign in tuberculosis. Charosky,[20] in a study of 240 patients, found the greatest increase in the metabolic rate in patients with active fibrocaseous lesions. McBrayer [21] and Moraldi [22] found an increased rate in a large percentage of their patients.

On the other hand, Izzo, Lanz and Casanegra [23] found the basal metabolic rate within normal limits in 83 per cent of 116 cases and concluded that when an elevation occurs it is in proportion to the elevation of the temperature. They said they felt that pulmonary tuberculosis itself does not exert any effect on basal metabolism. McCann and Barr [24] stated that the basal metabolic rate may be normal or slightly increased in tuberculosis and that in this disease the loss of weight may cause a drop in the metabolic rate which more than compensates for the tendency to an increase in the rate caused by the infection. Olivier and Skladal [25] found no correlation between the elevation of the basal metabolic rate and the severity of the tuberculosis and concluded that a normal rate does not necessarily indicate a stabilization of the tuberculous process. McMahon [26] found an increased basal metabolic rate only in cases of advanced tuberculosis. Marsh [27] reported normal rates in cases of advanced tuberculosis. Mäkinen [28] compared findings for 142 patients with pulmonary tuberculosis (928 determinations) with those for 10 normal subjects (75 determinations). He

19. Cordier, V.: Métabolisme basal des tuberculeux, Compt. rend. Soc. de biol. **88**:782, 1923.

20. Charosky, Leon: Metabolismo basal en la tuberculosis pulmonar: Consideraciones sobre 240 casos, Rev. Asoc. méd. argent. **48**:1256, 1934.

21. McBrayer, R. A.: Blood Sugar and Basal Metabolism Findings in Chronic Pulmonary Tuberculosis and Hyperthyroidism, J. A. M. A. **77**:861 (Sept. 10) 1921.

22. Moraldi, M.: Osservazioni sul metabolismo basale nella tubercolosi pulmonare, Tuberculosi **24**:329, 1932.

23. Izzo, R. A.; Lanz, P., and Casanegra, A.: El metabolismo basal en la tuberculosis pulmonar, Semana méd. **2**:1092 (Oct. 11) 1934.

24. McCann, W. S., and Barr, D. P.: Clinical Calorimetry: XXIX. The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Dec.) 1920.

25. Olivier, H. R., and Skladal, J.: Étude du métabolisme basal dans 30 cas de tuberculose pulmonaire, Ann. de méd. **34**:307, 1933.

26. McMahon, A.: Basal Metabolism in Pulmonary Tuberculosis, Tr. Am. Therap. Soc. **31**:221, 1931.

27. Marsh, M. E.: Respiratory Metabolism and Pulmonary Ventilation in Pulmonary Tuberculosis, J. Lab. & Clin. Med. **18**:599, 1933.

28. Mäkinen, N.: Beiträge zur Kenntnis über der Grundumsatz bei Lungentuberkulose, Acta Soc. med. fenn. duodecim (Ser. B, pt. 1, Art. 1) **18**:1, 1933.

found no correlation between the metabolic rate and the stage or pathologic type of tuberculosis or the sedimentation rate.

*Cholesterol Content of the Blood in Tuberculosis.*—The cholesterol content of the blood is almost constantly increased in hypothyroidism and is often decreased in hyperthyroidism.[29] Variations in the cholesterol content in tuberculosis are of interest and of possible importance in connection with these facts, although further study is necessary to determine any significant relation. It is generally agreed [30] that in active tuberculosis the cholesterol level is lowered, the lowest figure being obtained in the ulcerative forms with exudation.[30c] Healing is accompanied with a rising level. Lumbreras and Morante [30c] stated that a rise occurs also in tuberculous meningitis. They found no relation between the cholesterol content of the blood and the sedimentation rate or the bacillary content of the sputum and no definite relation between blood sugar and blood cholesterol in tuberculosis. Leonardi [30a] stated as his opinion that the body defenses are augmented by hypercholesteremia and that an increase in the ratio between cholesterol ester and free cholesterol is a favorable prognostic sign. Osato, Kurashige and Sakurai [31] found an increase in the fatty acid and cholesterol contents of the lungs and liver of tuberculous subjects, with a marked increase in the adrenal glands. Steinberg [30d] reported a fall in blood cholesterol values within forty-five days ante mortem in 17 of 20 persons dying of tuberculosis.

*Thyroid Opotherapy in Tuberculosis.*—Greenfield,[32] in 1893, and Morin,[33] in 1895, suggested the administration of thyroid substance in the treatment of tuberculous patients. A similar suggestion was made

29. Hurxthal, L. M.: Blood Cholesterol and Thyroid Disease: Myxoedema and Hypercholesteremia, Arch. Int. Med. **53**:762 (May) 1934.

30. (*a*) Leonardi, S.: La colesterina nel sangue e nell'espettorato dei tubercolotici polmonari, Morgagni **77**:683 (June 23) 1935. (*b*) Ceccarelli, Danilo: Ricerche sulla colesterinemia nei soggetti affetti da tuberculosi polmonare, Tubercolosi **25**:414, 1933. (*c*) Lumbreras, R. B., and Morante, A. F.: Colesterinemia y glicemia en los enfermos tuberculosis, Arch. de med., cir. y especialid. **37**:1365 (Dec. 15) 1934. (*d*) Steinberg, I. R.: La colesterinemia en los períodos preagónicos de la tuberculosis, Semana méd. **2**:1225 (Oct. 24) 1935. (*e*) Eyzaguirre y E., G.: La colesterina en la tuberculosis pulmonar, Crón. méd., Lima **53**:3, 1936.

31. Osato, S.; Kurashige, T., and Sakurai, H.: Fettstoffwechsel des tuberkulösen Organismus: I. Mitteilung; Untersuchungen über die Fett- und Lipoidverteilung in den Organen und Geweben des tuberkulösen Organismus, Jap. J. M. Sc. (VIII, Int. Med., Pediat. & Psychiat.) **4**:123, 1936.

32. Greenfield, W. S.: Some Diseases of the Thyroid Gland, Lancet **2**:1553, 1893.

33. Morin: Physiologie et médication thyroïdiennes, Rev. med. de la Suisse Rom. **15**:241 (May 20) 1895.

by Webb and his associates [34] in 1921. Coulaud [35] reported on 3 patients with nontuberculous arthritis in whom active pulmonary tuberculosis developed after they received thyroid therapy; he quoted references to 3 similar cases reported in the literature. Dalto and Charosky [36] gave 0.2 Gm. of a thyroid preparation daily for five days to 31 patients with pulmonary tuberculosis; only 3 showed a rise in pulse rate. Several writers have commented on the susceptibility of persons with hypothyroidism to tuberculosis. Schedtler,[9] however, found no such relation and stated that there is no basis for the treatment of tuberculous patients with thyroxin.

*Pathologic Picture of the Thyroid Gland in Tuberculosis.*—The subject of tuberculosis of the thyroid gland has been so extensively reviewed [37] that it requires only brief mention here. This condition is relatively rare (0.1 per cent of 20,758 glands examined at the Mayo Clinic [37a]), it affects women chiefly and it has a varied symptomatology, seldom being diagnosed clinically. It may be associated with toxic or nontoxic goiter, but whether coincidentally or as an etiologic agent is uncertain. It is believed to be hematogenous and usually secondary to a tuberculous focus elsewhere. Diffuse or isolated tubercles, caseation, abscess or diffuse sclerosis may be present. Of 125 cases, reports of which were collected by Rankin and Graham,[37a] active tuberculosis was known to be present in 6 and to be suspected in 5 others.

Coulaud [38] studied the thyroid glands of 120 tuberculous patients, with the findings presented in table 1. He stated that he had never seen the histologic picture of hyperthyroidism in the thyroid gland of a tuberculous subject. Roger and Garnier [39] reported marked sclerosis with periarteritis and endarteritis in the thyroid glands of 4 tuberculous subjects.

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34. Webb, G. B.; Gilbert, G. B., and Ryder, C. T.: The Adrenals and Thyroid in Experimental Tuberculosis, Am. Rev. Tuberc. **5**:266, 1921.

35. Coulaud, E.: L'opothérapie thyroïdienne et tuberculose, Ann. de méd. **10**: 385, 1921.

36. Dalto, A., and Charosky, L.: La prueba de la tiroidina en la tuberculosis pulmonar, Prensa méd. argent. **20**:1593 (July 19) 1933.

37. (*a*) Rankin, F. W., and Graham, A. S.: Tuberculosis of the Thyroid Gland, Ann. Surg. **96**:625, 1932. (*b*) Coller, F. A., and Huggins, C. B.: Tuberculosis of the Thyroid Gland, ibid. **84**:804, 1926. (*c*) Starlinger, F.: Cases of Tuberculosis of the Thyroid Gland, Wien. med. Wchnschr. **83**:439, 1933. (*d*) Sehmisch, W.: Schilddrüsentuberkulose und Basedow, Deutsche Ztschr. f. Chir. **243**:693, 1934. (*e*) Jedlička.[3]

38. Coulaud, E.: Le corps thyroïde des tuberculeux, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:1551 (Dec 17) 1920.

39. Roger, H., and Garnier, M.: La sclérose des corps thyroïdes chez les tuberculeux, Compt. rend. Soc. de biol. **5**:873, 1898.

From Jan. 1, 1930, to Sept. 1, 1936, 7,763 necropsies were performed in the University of Pennsylvania service at the Philadelphia General and University of Pennsylvania hospitals; 1,268 of these were on persons who died of tuberculosis or its complications. In 108 of the reports the thyroid gland was described either grossly or microscopically. The data are presented in table 2. It will be seen that no instance of hyperthyroidism and coexistent active pulmonary tuberculosis was found. During the same period necropsy was performed on 18 persons who died

TABLE 1.—*Pathologic Changes in the Thyroid Gland in Tuberculosis (Coulaud)*

| Pathologic Changes | Number of Patients |
|---|---|
| Tuberculosis | 3 |
| Cystic goiter | 3 |
| No definite change | 12 (most rapidly fatal tuberculosis) |
| Increased connective tissue (slight) | 14 |
| Large areas of sclerosis (patchy) | 6 |
| Diffuse sclerosis | 35 (mostly chronic tuberculosis) |
| Regeneration | 45 (slow involution of tuberculosis in most) |
| Phlegmon | 2 |

TABLE 2.—*Condition of Thyroid Glands of One Hundred and Eight Patients Who Died of Pulmonary Tuberculosis or Its Complications*

| | Type of Tuberculosis | | | | | |
|---|---|---|---|---|---|---|
| | Active (Adults) | | Healed (Adults) | | Active (Children) | Miscellaneous (Pleurisy, etc.) |
| Condition of Thyroid Gland | Gross | Microscopic | Gross | Microscopic | Microscopic | Microscopic |
| Normal | 50 | 9 | 4 | 4 | 2 | .. |
| Colloid goiter | .. | 1 | .. | .. | .. | .. |
| Fibrosis | .. | 2 | .. | 1 | .. | 1 |
| Hypoplasia | .. | 1 | .. | .. | .. | .. |
| Calcification | 1 | .. | .. | .. | .. | .. |
| Atrophy and fibrosis | 4 | 6 | .. | .. | .. | .. |
| Acute congestion | .. | 1 | .. | .. | .. | .. |
| Adenomatosis | 2 | 2 | .. | .. | .. | .. |
| "Degeneration" | .. | 1 | .. | .. | .. | .. |
| Chronic thyroiditis | .. | 1 | .. | .. | .. | .. |
| Hypertrophy | 1 | .. | 1 | .. | .. | .. |
| Adenoma with fibrosis | .. | 1 | .. | .. | .. | .. |
| Atrophy | 1 | .. | 1 | .. | .. | .. |
| Toxic hyperplasia | .. | .. | .. | 1 | .. | .. |

of hyperthyroidism or its complications. Among these, 2 showed healed apical tuberculosis, 1 a healed Ghon tubercle of the lower lobe and 1 tuberculous mediastinal adenitis. No instance of active pulmonary tuberculosis was found.

*Hyperthyroidism and Pulmonary Tuberculosis.*—Most writers agree that the association of frank hyperthyroidism with active pulmonary tuberculosis is uncommon. The incidences reported vary from 0.25 [40]

40. von Massur, F. W.: Relation of Thyroid Changes to Origin and Course of Chronic Pulmonary Tuberculosis, Beitr. z. Klin. d. Tuberk. **39**:45, 1918-1919.

to 15 per cent.[4b] Rink [41] reported an incidence of less than 1 per cent in 12,976 cases of pulmonary tuberculosis. The appearance of a mild transient picture of hyperthyroidism (forme fruste) with goiter and elevation of the basal metabolic rate is not uncommon, however, early in tuberculosis, especially in young women. This has been regarded as evidence of an active defense mechanism and has been correspondingly thought to be of good prognostic significance.[42] The signs and symptoms usually subside as the tuberculous lesion either progresses or heals. Steck [43] studied the reenforcing effect on epinephrine vasoconstriction of blood from normal persons, thyrotoxic patients and tuberculous patients with and without "Basedow-like" symptoms. He concluded that the thyroid gland does not play a part in producing the "thyrotoxic" symptoms often seen in tuberculosis. The difficulty of making a differential diagnosis between hyperthyroidism and early tuberculosis has received much attention.[44] Many of the signs and symptoms of early tuberculosis (tachycardia, loss of weight, nervousness and vasomotor phenomena) have been ascribed to a direct stimulating effect of the infection on the thyroid gland.[45] Pulmonary tuberculosis is regarded as an important and often overlooked cause of hyperthyroidism by some writers.[46] Others [47] believe that no significant relation exists between the two diseases.

Opinion is divided as to the effect of hyperthyroidism on the prognosis of coexistent tuberculosis. Fishberg,[48] Rink,[41] Lisser,[44b] Rich-

41. Rink, W.: Lungentuberkulose und Schilddrüsenerkrankungen, Tuberkulose **13**:179, 1933.

42. (*a*) Richard, G.: Syndromes basedowiens et tuberculose, Rev. franç. d'endocrinol. **12**:199, 1934. (*b*) Leitner, J.: Tuberkulose und innere Sekretion, Zentralbl. f. d. ges. Tuberk.-Forsch. **41**:1, 1935.

43. Steck, H.: Recherches expérimentales sur les relations hypothétiques entre la maladie de Basedow et la tuberculose, Schweiz. med. Wchnschr. **51**:535 (June 9) 1921.

44. (*a*) Stévenin, H., and Franchel, F.: Hyperthyroïdie et tuberculose pulmonaire, Monde méd., Paris **46**:649 (April 15) 1936. (*b*) Lisser, H.: The Relation of the Ductless Glands to the Incidence and Development of Tuberculosis, Am. Rev. Tuberc. **29**:249, 1934. (*c*) Frank, L. W.: Tuberculosis and Toxic Goiter, ibid. **25**:49, 1932. (*d*) Roberts, S. R.: The Determination of Tuberculosis and Toxic Goiter, ibid. **23**:120, 1931.

45. Marañón, G.: Hipertiroidismo y tuberculosis, Crón. méd. mex. **31**:829 (Sept.) 1932. Epstein.[4b]

46. Saathof, L.: Thyreosis und Tuberkulose, München. med. Wchnschr. **60**: 230, 1913.

47. Grüner, S.: Die Beziehungen zwischen Lungentuberkulose und den Erkrankungen der Thyreoidea, Ztschr. f. Tuberk. **53**:319, 1929.

48. Fishberg, M.: Pulmonary Tuberculosis, ed. 4, Philadelphia, Lea & Febiger, 1932, vol. 2, pp. 217-219.

ard [42a] and others have stated the opinion that the course of tuberculosis is favorable when hyperthyroidism is present. Lisser [44b] and Fishberg [48] have emphasized the susceptibility of myxedematous persons to tuberculosis. A corollary to these views is the belief that tuberculous patients with toxic goiter should be treated conservatively and that thyroidectomy in such cases is likely to be followed by rapid progress of the pulmonary process.[49] On the contrary, hyperthyroidism is regarded by several authors [50] as an aggravating factor. Thyroidectomy has been advocated by Crile,[51] Cattell and Meredith,[52] Roberts,[44d] Sloan [53] and others. Crile reported that of 87 patients with tuberculosis and hyperthyroidism, 74.5 per cent of those in whom the diagnosis of tuberculosis was confirmed roentgenographically showed definite improvement after thyroidectomy. Of those followed postoperatively by means of roentgenograms, 82 per cent showed improvement and 35 per cent cure.

## REPORT OF CASES

During the period from Jan. 1, 1930, to Sept. 1, 1936, 1,053 patients with hyperthyroidism were admitted to the Hospital of the University of Pennsylvania. Among them were 14 with pulmonary tuberculosis (diagnosis based on roentgen findings and positive results of examination of the sputum or physical signs), an incidence of 1.3 per cent. During approximately the same period (Jan. 1, 1930, to Dec. 1, 1936), among 729 patients with pulmonary tuberculosis, active and arrested, the incidence of hyperthyroidism (14 cases) was 1.9 per cent.[54]

We have reviewed the records of 23 thyrotoxic patients with associated pulmonary tuberculosis who were admitted to the hospital between

49. Hoffmann, H.: Goiter and Tuberculosis, München. med. Wchnschr. **70**: 1363, 1923.

50. Coulaud, E.: Corps thyroïde et tuberculose, Thesis, Paris, Vigot frères, 1922. Sergent, E., and Mignot, R.: Hyperthyroïdie et tuberculose pulmonaire, Rev. de la tuberc. **6**:561, 1925. Ison, H. L.: Hyperthyroidism in Tuberculosis, M. Bull. Vet. Admin. **7**:1171, 1931.

51. Crile, G. W.: Hyperthyroidism and Associated Diseases, Surg., Gynec. & Obst. **58**:272, 1934.

52. Cattell, R. B., and Meredith, J. M.: The Management of Concomitant Hyperthyroidism and Pulmonary Tuberculosis, S. Clin. North America **16**: 1537, 1936.

53. Sloan, E. P.: Tuberculosis and Goiter, J. A. M. A. **88**:1954 (June 18) 1927.

54. The mortality from tuberculosis for the United States registration area is about 59 per 100,000. Although there are no accurate statistics on the number of cases of active tuberculosis—the morbidity rate—it is generally agreed that this figure is at least ten times the mortality rate. A conservative estimate therefore would be that the morbidity rate is at least 590, or practically 0.6 per cent, for the country as a whole. The figure is fairly uniform for the various sections of the country where tuberculosis is a reportable disease.

June 1924 and October 1935. Whenever possible these patients have been brought back for follow-up examination, which has included the making of roentgenograms of the chest, blood counts, estimations of the sedimentation rate, determinations of the basal metabolic rate, examinations of the sputum when feasible and physical examinations; with the aid of these findings and the interval history the progress of the two diseases has been determined.

For purposes of analysis the patients have been divided into two groups. Group 1 contains 10 patients in whom tuberculosis was considered active when they were first seen. Group 2 contains 13 patients in whom tuberculosis was considered inactive when they were first seen. Six patients died of tuberculosis from a month to eight and one-third years after admission to the hospital. One patient died of a fractured skull. There were no deaths attributable to hyperthyroidism. The patients were referred back to their physicians or to sanatoriums for treatment of the tuberculosis. There was no evidence of extrapulmonary tuberculosis in any patient at the time of admission to the hospital. No evidence of tuberculosis was seen in any of the thyroid glands removed at operation; serial sections, however, were not made. All patients operated on received iodine (compound solution of iodine or potassium iodide) as part of their preparation. A local anesthetic was employed, supplemented by nitrous oxide or avertin.

The pertinent data relating to our patients are presented in tables 3 and 4 and are summarized in table 5. It will be seen that all the patients in group 1 were women, most of them (7 of 10) under 40 years of age. In these patients the response of the hyperthyroidism to treatment was not as good as is to be expected in cases of ordinary uncomplicated hyperthyroidism, only 3 patients being completely relieved and 1 remaining unimproved. Treatment of the hyperthyroidism likewise did not, in general, favorably affect the pulmonary disease; only 2 patients showed slight improvement, and 3 died of tuberculosis, the remainder becoming worse or remaining unchanged. One patient showed an acute postoperative exacerbation of the tuberculosis. The patients in group 2 were older, only 4 being under 40. The effects of treatment on the hyperthyroidism were definitely better than in the patients in group 1. The course of the tuberculous processes was likewise more favorable. Although 3 patients died of the pulmonary disease after activation (which occurred from three to seventy-nine months after thyroidectomy), 4 showed healing and 2 improvement. The preoperative response to iodine was somewhat better than that of the patients in group 1.

For many years it has been believed that the administration of iodides is contraindicated in tuberculosis because of the danger of pro-

TABLE 3.—*Clinical Data for Ten Patients with Pulmonary Lesions Considered Active When Patients Were First Seen*

| Patient | Age | Sex | Type of Goiter | Basal Metabolic Rate, % | Location of Lesion (Roentgenogram) | Physical Signs | Results of Examination of Sputum | Treatment of Thyroid Condition | Results | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Hyperthyroidism | Tuberculosis |
| F. D.* | 31 | F | Nodular | — 5 | Both upper lobes | Present | Positive, late | Subtotal thyroidectomy | Improved for 4 mo. | Died 52 mo. after operation |
| E. M.* | 32 | F | Diffuse | +74 | Entire left lung (pneumonia) | Present | Positive | Irradiation; iodine | Unimproved | Died 1 mo. after admission |
| L. S. | 33 | F | Diffuse | +62 | Upper lobe of right lung | Present | Positive | Two stage thyroidectomy | Improved | Died 18 mo. after first operation |
| E. S.* | 24 | F | Nodular | +39 | Both upper lobes | Present | None | Lobectomy | Improved | Slight progression 87 mo. after operation |
| V. S. | 38 | F | Diffuse | +52 | Upper lobe of right lung | Present | Negative | Subtotal thyroidectomy | Improved for 2½ mo. | Unknown; patient not seen after 2½ mo. |
| E. H. | 44 | F | Diffuse | +53 | Both upper lobes | Present | Negative | Subtotal thyroidectomy | Cured | Slight improvement 5 mo. after operation |
| C. D. | 42 | F | Diffuse | +62 | Upper lobe of right lung | Present | Negative | Two stage thyroidectomy; irradiation; iodine | Partial improvement; recurrence after operation | Slight progression 74 mo. after first operation |
| I. L. | 24 | F | Diffuse | +45 | Both upper lobes | Present | None | Two stage thyroidectomy; irradiation; iodine | Improved | No marked change; tuberculosis first found during postoperative recurrence of hyperthyroidism |
| B. G. | 63 | F | Diffuse | +40 | Both upper lobes | Questionable | Negative | Subtotal thyroidectomy | Cured | No change 13 mo. after operation |
| E. N. | 32 | F | Diffuse | +31 | Upper lobe of right lung | None | None | Iodine; irradiation | Cured | Improved 57 mo. after treatment was begun |

* See discussion in the text.

TABLE 4.—*Clinical Data for Thirteen Patients with Pulmonary Lesions Considered Inactive or Doubtfully Active When Patients Were First Seen*

| Patient | Age | Sex | Type of Goiter | Basal Metabolic Rate, % | Location of Lesion (Roentgenogram) | Physical Signs | Results of Examination of Sputum | Treatment of Thyroid Condition | Results | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Hyperthyroidism | Tuberculosis |
| I. M. | 60 | M | Diffuse | +41 | Both upper lobes | Questionable | Negative | Two stage thyroidectomy | Cured | Lesion disappeared 64 mo. after operation |
| J. D. | 65 | F | Diffuse | +37 | Upper lobe of left lung | None | None | Subtotal thyroidectomy | Marked improvement 4 mo. after operation | Unknown; patient not seen after 4 mo. |
| I. E. | 45 | F | Diffuse | +50 | Both upper lobes | None | None | Subtotal thyroidectomy | Cured (mild postoperative hypothyroidism) | Lesion had disappeared 7 yr. after operation |
| J. A. | 41 | M | Diffuse | +35 | Upper lobe of left lung | None | None | Irradiation | Cured (mild symptoms) | Lesion almost disappeared 3 yr. after treatment |
| M. F. | 51 | F | Nodular | +49 | Both upper lobes | Present (upper lobe of right lung) | None | Bipolar ligation | Cured | Died of tuberculosis 100 mo. after operation; acute exacerbation 72 mo. after operation |
| A. M. | 34 | F | Diffuse | +32 | Upper lobe of right lung | Questionable | None | Lobectomy | Marked improvement 8 mo. after operation | Acute exacerbation 39 mo. after operation; died 52 mo. after operation |
| B. F. | 57 | F | Nodular | — 1 | Lower lobe of left; upper lobe of right lung | None | None | Lobectomy | Clinically relieved but metabolic rate up to +24% 34 mo. after operation | Slight progression 34 mo. after operation |
| C. H. | 32 | M | Nodular | +52 | Both upper lobes | Present (upper lobe of right lung) | None | Lobectomy | Cured | Marked improvement 78 mo. after operation |
| K. W. | 44 | F | Diffuse | +44 | Both upper lobes | Questionable in upper lobe of right lung | None | Irradiation | Cured | Healed 72 mo. after treatment |
| D. L. | 48 | M | Diffuse | +70 | Both upper lobes | Present | Negative | Two stage thyroidectomy | Marked improvement | Improved 96 mo. after operation |
| A. K. | 48 | F | Nodular | +31 | Upper lobe of right lung | None | None | Subtotal thyroidectomy | Cured 7 mo. after operation | No change; died of skull fracture 9 mo. after operation |
| C. H. | 37 | F | Diffuse | +26 | Upper lobe of right lung | None | None | Subtotal thyroidectomy | Cured 7 mo. after operation | Progression 7 mo. after operation |
| G. L. | 30 | F | Nodular | +45 | Upper lobe of left lung | Questionable | Negative until exacerbation | Subtotal thyroidectomy | Improved | Activation with rapid spread through left lung and death 9 mo. after operation |

ducing an acute flare-up or extension. We have reviewed the records of all our patients (20) who received iodine for evidence of such an untoward effect without finding any clear evidence that the tuberculosis was influenced unfavorably. One patient showed an exacerbation soon after thyroidectomy, and 1 patient, desperately ill with tuberculous pneumonia and presenting a clinical picture of fulminating hyperthyroidism (to be discussed), failed to respond to iodine. In neither case, however, could iodine be blamed with certainty, as several other factors were involved.

TABLE 5.—*Summary of Data in Tables 3 and 4*

| | Number of Patients | |
|---|---|---|
| | Active Tuberculosis | Inactive Tuberculosis |
| Sex: | | |
| Males | 0 | 4 |
| Females | 10 | 9 |
| Follow-up period | 1 to 87 mo. | 4 to 100 mo. |
| Treatment of hyperthyroidism: | | |
| Irradiation | 2 | 2 |
| One stage thyroidectomy | 4 | 5 |
| Two stage thyroidectomy | 3 | 2 |
| Lobectomy or adenectomy | 1 | 3 |
| Bipolar ligation | .. | 1 |
| Effect of iodine on hyperthyroidism: | | |
| Favorable | 7 | 10 |
| Questionable | 2 | 1 |
| None | 1 | .. |
| Immediate postoperative course: | | |
| Normal | 5 | 8 |
| Unexplained fever | 2 | 2 |
| Exacerbation of tuberculosis | 1 | .. |
| Acute nontuberculous infection of respiratory tract | .. | 1 |
| Course of tuberculosis after treatment of hyperthyroidism: | | |
| No change | 3 | 1 |
| Healed | .. | 4 |
| Improved | 2 | 2 |
| Worse | 1 | 2 |
| Died | 3 | 3 |
| Unknown | 1 | 1 |
| Effect of treatment on hyperthyroidism: | | |
| Cured | 3 | 10 |
| Improved | 6 | 3 |
| Unimproved | 1 | .. |

Except for somewhat prolonged febrile periods in 4 cases, 1 case of acute nontuberculous infection of the respiratory tract and 1 case of acute exacerbation of tuberculosis, the 19 patients operated on had an immediate postoperative course which was uneventful.

We wish to call attention to 3 patients, all with active pulmonary lesions, who showed the clinical phenomena of hyperthyroidism but whose thyroid glands did not show the histologic picture either of thyrotoxicosis or of iodine response. Two showed "colloid adenomas" (possibly areas of cyclic hyperinvolution containing excess colloid). One of these patients had a normal basal metabolic rate but in all other respects appeared clinically thyrotoxic; she showed improvement, with

a gain of 11 pounds (5 Kg.) four months after operation, but subsequently died of tuberculosis. The other patient had a basal metabolic rate of + 39 per cent; her thyrotoxic symptoms were improved seven and one-fourth years after operation, but the tuberculosis had progressed somewhat.

The third patient was a woman of 30 who had lost weight and had shown signs of nervousness for two or three years. A cough had been present for a month. She showed exophthalmos, goiter, auricular fibrillation, tremor and vasomotor changes, and the basal metabolic rate was + 74 per cent. Soon after she was hospitalized there developed consolidation of the lower lobe of the left lung and coincidentally glycosuria and hyperglycemia. The sputum contained large numbers of tubercle bacilli. The pulmonary process spread rapidly throughout the entire left lung. The thyrotoxic symptoms did not respond to iodine or small doses of roentgen rays, and she died one month after admission to the hospital. Necropsy showed tuberculous pneumonia involving the entire left lung. The thyroid gland showed no histologic evidence of toxic hyperplasia or iodine response; the appearance was that of a colloid goiter with fibrosis.

These cases lend some support to the possibility that the clinical picture of hyperthyroidism may be produced by the action of the tuberculotoxin in stimulating the thyroid gland without producing the structural changes characteristic of toxic goiter.

Our experience suggests that the coexistence of hyperthyroidism and pulmonary tuberculosis is commoner than has generally been believed, at least in a metropolitan population (all our patients lived in or near Philadelphia). We could not obtain clear evidence from our patients' histories as to which of the diseases tended to appear first, although tuberculosis was not suspected in 15 of the 23 cases when the patient was first referred for treatment of hyperthyroidism. The progress of our patients definitely suggests that the relief of hyperthyroidism did not influence favorably the prognosis of the pulmonary lesion. Conversely, the presence of active tuberculosis seemed to impair slightly the prospect for complete cure of coexistent hyperthyroidism (table 5).

## SUMMARY

The more important literature relating to various aspects of the relation between the thyroid gland and tuberculosis has been briefly reviewed.

The clinical incidence of pulmonary tuberculosis in hyperthyroidism and of hyperthyroidism in pulmonary tuberculosis at the Hospital of the University of Pennsylvania over a period of sixty-eight months is reported.

The changes observed in the thyroid gland at necropsy on 108 persons with pulmonary tuberculosis and the incidence of tuberculosis at necropsy on 18 thyrotoxic patients are reported.

The significant data relating to 23 patients with associated hyperthyroidism and pulmonary tuberculosis are presented and discussed.

## CONCLUSIONS

Our series of cases is too small to warrant any generalizations, but our experience suggests the following conclusions:

The administration of iodine to thyrotoxic patients with pulmonary tuberculosis does not tend to precipitate any immediate exacerbation or extension of the tuberculosis.

An operation on the thyroid gland is usually well tolerated by patients with pulmonary tuberculosis.

The coexistence of pulmonary tuberculosis does not impair materially the prospect for the successful treatment (irradiation or operation) of hyperthyroidism.

The relief of hyperthyroidism does not seem to influence favorably the prognosis for patients with associated active pulmonary tuberculosis.

The clinical picture of hyperthyroidism, without characteristic structural changes in the thyroid gland, may occur in patients with active pulmonary tuberculosis.

Dr. E. B. Krumbhaar, of the Department of Pathology, the University of Pennsylvania School of Medicine, gave us permission to review the necropsy records. Dr. Thomas Fitz-Hugh Jr. gave us permission to include 1 of his private patients in our series.

# PROLONGED MENINGOCOCCEMIA

## REPORT OF THREE CASES

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The recognition of meningococcic septicemia is an achievement of the twentieth century. Although the causative organism of meningitis was recognized and described by Weichselbaum in 1887, it was not until Gwyn's [1] report in 1899 that the meningococcus was demonstrated in the blood. Since the beginning of this century the American literature has contained many reports of extrameningeal types of meningococcic infection, but there have been relatively few reports of prolonged meningococcemia.

In the early part of this century it was believed by many that meningococcic septicemia if it occurs at all only follows an attack of meningitis and that the eruption so frequently seen in cases of meningitis is caused by a circulating toxin. Experience during and since the World War has led to acceptance of the belief so ably set forth by W. W. Herrick [2] in 1919. He divided meningococcic sepsis into three stages: The first stage is one of local infection of the upper respiratory passages, lasting two days to six weeks. The second is one of general invasion of the blood stream, usually lasting forty-eight hours. Finally, there is the stage of metastatic localization of the organisms in the meninges or other organs as the third and last stage.

It has now become a well established fact that an infection caused by the meningococcus may reach the second stage and go no farther, and, indeed, there are now enough examples to demonstrate that prolonged meningococcic infection of the blood is a definite disease entity. The time-honored tendency to associate all meningococcic infections with "epidemic cerebrospinal meningitis" has naturally obscured this group

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From the Medical Service of the Walter Reed General Hospital.

1. Gwyn, N. B.: A Case of General Infection by the Diplococcus Intracellularis Weichselbaum, Bull. Johns Hopkins Hosp. **10**:112-113 (June) 1899.

2. Herrick, W. W.: Extrameningeal Meningococcus Infections, Arch. Int. Med. **23**:409-418 (April) 1919.

of extrameningeal infections. It is therefore urged that this term be abandoned in favor of the more generically correct term meningococcic meningitis.

The first case of prolonged meningococcemia was reported by Solomon,[3] in Germany, in 1902. The following summary was taken from the discussions by Bovaird [4] and Bray.[5] This patient, a woman of 32 years, suffered for two months with intermittent chills, fever, rash, myalgia and arthralgia. Culture of the blood yielded meningococci, and it was not until two months after the onset that meningitis supervened. She recovered after an illness of four months.

## REPORT OF CASES

CASE 1.—T. M., a private, stationed at Fort Mason, Calif., was admitted to the Letterman Hospital on June 2, 1929, with the complaint of sudden onset of chills, vertigo, headache and pain in the abdomen. He had a temperature of 103 F. Examination revealed a scanty macular rash over the abdomen and extremities and moderate leukocytosis. Six days after his admission to the hospital culture of the blood yielded meningococci. From June 12 to 23 a total of 500 cc. of antimeningococcus serum was given intravenously in ten injections of 50 cc. each, but the patient's condition remained essentially unchanged and the fever persisted, being of an intermittent septic type. Thirty-three days after the onset, the patient suffered from intense headache, nausea and vomiting. He had definite signs of meningitis, and the spinal fluid contained 6,000 white blood cells, with 80 per cent polymorphonuclears. An additional 130 cc. of antimeningococcus serum was given intrathecally, and the patient made a complete recovery.

CASE 2.—E. H. P., a private, stationed at Fort Howard, Md., suddenly became ill on May 3, 1936, with recurring attacks of chills and fever. He was admitted to the station hospital on May 10. For six weeks he had an intermittent fever (the temperature ranging from normal to 103 and 104 F.) which recurred every three or four days. During this time he noted frequent severe attacks of arthralgia and occasionally "spots" on his legs, but between the paroxysms of fever he was free from symptoms. Forty-three days after the onset of the illness, during one of the paroxyms of fever, he experienced an intense headache and became very ill. He was admitted to the Walter Reed Hospital on the same day, and it was immediately decided that he had meningitis. Lumbar puncture revealed cloudy fluid, a high leukocyte count and intracellular germ-negative diplococci on a smear. He was given 100 cc. of antimeningococcus serum intravenously and 240 cc. intraspinally. He made a complete recovery after an illness of seven weeks.

CASE 3.—M. W. T., a captain aged 33, was admitted to the Walter Reed Hospital on April 2, 1936, the diagnosis which was made before transfer being acute rheumatic fever. The past history was noncontributory except for the fact that one month prior to his admission to the hospital his left thumb had been bitten by his

3. Soloman, H.: Ueber Meningokokkenseptikämie, Klin. Wchnschr. **39**:1045, 1902.

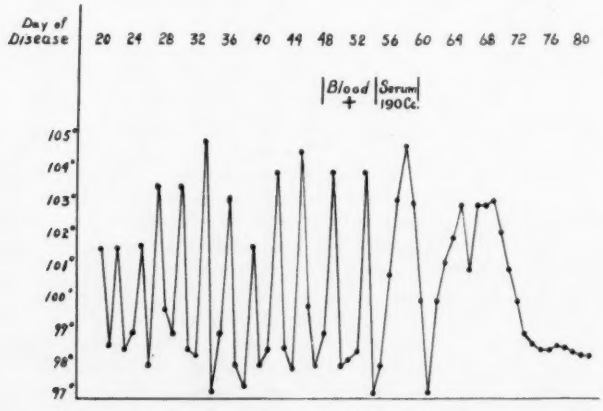
4. Bovaird, David, Jr.: Meningococcus Septicemia with Sterile Cerebrospinal Fluid: Iridocyclitis; Flexner's Serum; Recovery, Arch. Int. Med. **3**:267-278 (April) 1909.

5. Bray, H. A.: Chronic Meningococcus Septicemia Associated with Pulmonary Tuberculosis, Arch. Int. Med. **16**:487-502 (Sept.) 1915.

small dog. This lesion became infected and suppurated, but no swelling of the regional lymph nodes or general systemic reaction was noted.

*Present Illness.*—Twelve days prior to admission to the hospital the patient did not feel well. The following day he noted the onset of generalized aches and pains, with slight headache and sore throat. These symptoms subsided for three days, only to reappear and persist for seven days prior to his admission to the hospital. During the recrudescence the temperature rose to 103 or 104 F. once a day, and he had severe pains in the elbows, knees, shins, calves and ankles. A rash appeared which consisted of slightly swollen areas on the arms, chest and legs.

*Physical Examination.*—The patient was brought into the hospital on a litter. The temperature was 100 F., the pulse rate 100 and the respiratory rate 26. There was a generalized erythematous maculopapular rash over the arms, chest and legs. The lesions ranged from the size of a pinpoint to 1 or 1.5 cm. in diameter. A few of them had yellow raised centers. On the dorsum of the left thumb was an




Temperature curve for third patient.

exfoliating lesion about 3 cm. in diameter which was not suppurating. There was no general glandular enlargement, and the circulatory system was normal. The blood pressure was 120 systolic and 80 diastolic. No cardiac murmurs were noted. The lungs were clear to percussion and auscultation. The abdomen was flat and soft, and the spleen was not palpable. Neurologic examination revealed no abnormality.

*Laboratory Data.*—The blood always showed a normal red cell count. The white cell count ranged from 10,000 to 21,000. The Wassermann and Kahn reactions were negative. Roentgenograms of the chest, with cardiac measurements, were normal. Cultures of the blood made before May 8 were sterile, and repeated agglutination for the typhoid, paratyphoid, brucella, pasteurella and proteus groups gave negative results. Six intensive examinations of the blood revealed no malarial organisms. The possibility of relapsing fever or rat-bite fever was ruled out on the basis of animal inoculation. On May 5 the blood serum was found to agglutinate type II meningoccoci in a titer of 1 : 160. On May 8 blood collected by Col. Arthur P. Hitchins of the Army Medical School, and planted on Kracke's

culture medium of buffered tissue fluid [6] yielded the meningococcus. One subsequent culture of the blood was also positive for type II meningococcus.

*Course.*—During the first seven weeks of his illness the course was characterized by paroxysms of fever, occurring every third or fourth day, accompanied with marked prostration, myalgia, arthralgia, headache and rash. The severity of these attacks gradually increased, and occasionally the temperature reached 104 or 105 F. It was during this stage that several diagnoses were considered, including those of acute rheumatic fever, endocarditis due to Streptococcus viridans, malaria, undulant fever, rat-bite fever and finally meningococcemia.

On the fifty-fourth day of the illness it was learned that the patient had had injections of therapeutic horse serum on two previous occasions. He was found to be moderately sensitive, but, despite this, it was thought advisable to administer serum. A total of 190 cc. of a polyvalent antimeningococcus serum was given parenterally in divided doses. After severe serum sickness, the patient recovered without complications or sequelae. The duration of his illness was seventy days.

## COMMENT

From the reports of thirty-three cases collected from the American literature the average age was found to be 27.7 years, with extremes of 8.5 and 48 years. Twenty-three cases occurred in males.

*Incidence of Various Signs and Symptoms in Thirty-Three Cases of Meningococcemia*

| | Cases | | Cases |
|---|---|---|---|
| Rash | 30 | Sweating | 11 |
| Intermittent fever | 26 | Vomiting | 6 |
| Arthralgia | 23 | Sore throat | 5 |
| Chills | 21 | Epistaxis | 2 |
| Headache | 17 | Herpes | 2 |
| Myalgia | 12 | Bronchitis | 2 |

It was noted that the onset in the majority of these cases was described as sudden—within one or two days—and was characterized by headache, chills, fever, rash and aches and pains in the muscles and joints. Occasionally bronchitis, tonsillitis and pharyngitis were noticed. One case reported by Morgan [7] shortly followed the extraction of a tooth. Though one might expect to find sinusitis as a common symptom, definite sinal infection was demonstrated in only one case in this series.

The pains in the joints and muscles were such prominent features that the usual initial diagnosis was acute rheumatic fever. During the first week, however, it was commonly noted that the patients exhibited an intermittent type of fever, similar in many respects to either tertian or quartan malarial fever (chart). It was frequently so suggestive that

6. Simmons, J. S.: Laboratory Methods of the United States Army, Philadelphia, Lea & Febiger, 1935.

7. Morgan, Hugh J.: Chronic Meningococcus Septicemia, Bull. Johns Hopkins Hosp. **32**:245-254 (Aug.) 1921.

after a course of salicylates, quinine was often given in the face of an inability to demonstrate plasmodia in the blood. This likeness to the paludal types of fever has been especially commented on by Rolleston,[8] Dock,[9] Vesell and Barsky [10] and Bloedorn.[11]

The rash, recorded in thirty cases, consisted of multiform erythematous lesions, ranging from the size of a pinhead to 1.5 to 2 cm. in diameter. Occasionally, white raised centers were noted, but the most characteristic lesions were small pink papules with red centers, usually located on the arms, legs and chest. These lesions tended to come in crops just before or just after the fastigium of the paroxysm of fever. Good reproductions of these lesions can be found in the articles by Richter,[12] Harrison and Abernethy [13] and Brown.[14]

Certain other features of this type of septicemia deserve comment. The progressive secondary anemia that is so characteristic of other types of septicemia was rarely found. Severe cachexia was not the rule. Indeed, the patient often waited weeks before seeking medical aid because of the feeling of well-being between the paroxysms. Enlargement of the spleen, clubbing of the fingers, pallor of the skin, perisplenitis and hematuria, so characteristically found in the type of endocarditis due to Str. viridans, were infrequently encountered in meningococcemia. Jaundice was consistently not mentioned in the case reports of this disease. In our cases there was no disproportion between the temperature and the pulse rate. The average duration of the disease was eleven and nine-tenths weeks, with extremes of five and thirty-two weeks. There were three deaths in the thirty-three cases in this series, making a mortality of 9.1 per cent. Two of the patients died after the onset of meningitis.[15] The third case, though permission for necropsy was not granted, was probably complicated by endocarditis.[16] A fourth patient died of nephritis five months after recovery from meningococcemia.[13]

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8. Rolleston, Humphry: Lumleian Lectures on Cerebrospinal Fever, Lancet **1**:541-549 (April 5) 1919.

9. Dock, William: Intermittent Fever of Seven Months' Duration Due to Meningococcemia, J. A. M. A. **83**:31-33 (July 5) 1924.

10. Vesell, Harry, and Barsky, Joseph: Chronic Meningococcus Septicemia, Am. J. M. Sc. **179**:589-599 (May) 1930.

11. Bloedorn, W. A.: Meningococcus Septicemia, Am. J. M. Sc. **162**:881-891 (Dec.) 1921.

12. Richter, Arthur B.: Meningococcemia: Report of Two Cases with Recovery, J. A. M. A. **102**:2012-2015 (June 16) 1934.

13. Harrison, F. F., and Abernethy, T. J.: Chronic Meningococcemia, Clin. Misc., Mary I. Bassett Hosp. **1**:3-15, 1934.

14. Brown, C. L.: The Skin Lesions in Meningococcus Septicemia, Am. J. Dis. Child. **27**:598-602 (June) 1937.

15. Dock.[9] Vesell and Barsky.[10]

16. Hennell, Herman, and Wiener, Herbert J.: Report of a Case of Chronic Meningococcemia, M. J. & Rec. **131**:292-295 (March 19) 1930.

Much attention has been focused on the heart, and several cases of systolic murmurs were reported,[17] a few cases in association with cardiac enlargement.[18] Whether these findings are signs of real endocarditis or the effects of fever and toxemia cannot be settled here, though it should be pointed out that in the cases of meningococcic sepsis in which there are signs of congestive failure and cardiac incompetency, the mortality is high and in these cases definite vegetative endocarditis is always demonstrated at necropsy. The reader is urged to refer to the illustrated articles by Rhoads,[19] Bancker,[20] Gwyn [21] and Hyland [22] for further study of this phase of the subject. The dividing line between prolonged meningococcemia and meningococcic endocarditis is not an easy one to draw, and an overlapping of the cases cannot be avoided. There have been, however, as many as fourteen cases in which the clinical picture was primarily one of cardiac failure and in which the characteristic symptoms of prolonged septicemia were absent. For example, Cecil and Soper [23] reported a case in which the prolonged intermittent character of meningococcemia was absent. There was no rash until shortly before death, and the fever was of the high sustained type. The duration of illness in this case was twenty-four days, and at necropsy definite endocarditis was demonstrated. Warfield [24] reported the case of a 32 year old Negro who had been sick for one week before coming to the hospital. The initial symptoms consisted of headache, chills, cough and delirium. A palpable precordial thrill, a systolic murmur and an irregular pulse were noted when he was admitted. There was no rash or meningitis. After an illness of five weeks he died, and the necropsy showed vegetative endocarditis. A case of this type is primarily endocarditis and should not be included in a series of cases of prolonged meningococcemia.

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17. (*a*) Clark, Fred B.: Chronic Meningococcemia, California & West. Med. **34**:361-364 (May) 1931. (*b*) Master, Arthur M.: Meningococcemia with Endocarditis, J. A. M. A. **96**:164-166 (Jan. 17) 1931. (*c*) Bray.[5] Dock.[9] Hennell and Wiener.[16]

18. Henneli and Wiener.[16] Master.[17b]

19. Rhoads, C. P.: Vegetative Endocarditis Due to the Meningococcus, Am. J. Path. **3**:623-629 (Nov.) 1927.

20. Bancker, Evert A.: Meningococcus Endocarditis, J. M. A. Georgia **19**:480-485 (Nov.) 1930.

21. Gwyn, N. B.: Subacute Meningococcal Endocarditis, Arch. Int. Med. **48**: 1110-1117 (Dec.) 1931.

22. Hyland, C. M.: Meningococcus Endocarditis, J. A. M. A. **92**:1412 (April 27) 1929.

23. Cecil, Russell L., and Soper, Willard B.: Meningococcus Endocarditis, with Septicemia, Arch. Int. Med. **8**:1-16 (July) 1911.

24. Warfield, Louis M.: Acute Ulcerative Endocarditis Caused by the Meningococcus (Weichselbaum), Univ. Pennsylvania M. Bull. **16**:180-182 (July-Aug.) 1903.

There have been, however, at least four cases of prolonged meningococcemia in which there was evidence strongly suggesting the complication of acute endocarditis. The first case, reported by Hennell and Wiener,[16] was that of a man of 40 who gave a history of four weeks of intermittent attacks of chills, fever, sweats and rash, with the feeling of well-being between attacks. During the fourth week the rash, chills and sweats disappeared, and he became weak and was confined to bed. From then until death occurred the temperature remained continuously high. There were undoubted signs of endocarditis of the aortic and mitral valves, and even though permission for necropsy was not granted, it can be considered that this was a case of prolonged meningococcemia complicated by acute endocarditis. Master [17b] reported three cases in which there was presumptive evidence of acute endocarditis complicating prolonged meningococcemia. In these three cases recovery occurred after thorough treatment with serum. Consequently, absolute proof is lacking, but the data serve to emphasize the fact that there are a small group of borderline cases that reveal the relation of simple prolonged meningococcemia to endocarditis. They bear the same relation to each other that prolonged meningococcemia bears to meningococcic meningitis.

Headache was reported in seventeen of the cases and vomiting in six of the cases as the only symptom referable to the central nervous system that occurred prior to the onset of meningitis. When meningitis supervened it was always heralded by signs of severe meningeal irritation and increased intracranial pressure. Nineteen of the patients (57.5 per cent) of this series did not have meningitis. In fourteen patients (42.5 per cent) meningitis developed; in three patients meningitis developed before the prolonged septicemia set in,[25] in ten it developed late in the course of the septicemia and in one case there were two separate attacks.[26] Hemiplegia was a complication in Conklin's case.[27]

Anemia was not a prominent feature except in the three cases complicated by nephritis and the one complicated by Banti's splenic anemia.[28] A leukocyte count ranging from 10,000 to 20,000, with an increase of polymorphonuclears, was the usual finding, though in the one case of

25. (*a*) Maxcy, Kenneth F.: Observations on the Presence of Meningococcus in the Blood, J. Infect. Dis. **23**:470-474, 1918. (*b*) Seeley, Sam F.: Meningococcic Septicemia, Mil. Surgeon **71**:309-313 (Oct.) 1932. (*c*) Lemann, I. L., and Teasley, H. E.: Meningococcemia for Eight Months Following Meningitis: Recovery, New Orleans M. & S. J. **83**:448-453 (Jan.) 1931.

26. Graves, W. R.; Dulaney, Anna Dean, and Mickelson, I. D.: Chronic Meningococcemia, J. A. M. A. **92**:1923-1925 (June 8) 1929.

27. Conklin, Coursen B.: Meningococcemia, M. Ann. District of Columbia **4**: 313-315 (Dec.) 1935.

28. Binns, James F., and Fothergill, Leroy D.: Chronic Meningococcus Septicemia, New England J. Med. **205**:536-539 (Sept. 10) 1931.

Banti's disease leukopenia was present. It is interesting to note that after this patient recovered from the meningococcemia, splenectomy was accomplished, with consequent improvement of the patient.

The most important single factor in the diagnosis of meningococcemia is to have the disease in mind. In a few cases the condition was diagnosed within the first few days, but in the majority of cases three to five weeks elapsed before a diagnosis was made. It does not need to be emphasized that culture of the blood is the most useful of all laboratory procedures in making a diagnosis, but it must be stressed that the usual beef broth and agar are poor mediums in which to grow the meningococcus from the blood.[29] In order to insure prompt growth, the medium should be especially enriched with ascitic fluid or blood serum. Negative results of culture, even with enriched mediums, do not exclude meningococcemia, because several cases have been reported in which especially enriched mediums were used and positive results were not obtained until after the fifteenth day.[30] In case 3 of our series the first positive evidence of meningococcemia was obtained from blood agglutination against stock meningococci. This procedure should be carried out whenever feasible as it may prove to give valuable confirmative evidence. After the organism has been recovered from the blood, it should be differentiated from the gonococcus by the sugar fermentation test and then agglutinated by the different commercial polyvalent antimeningococcus serums in various dilutions in order to determine the best serum to use in treatment. According to Herrick,[2] the commercial serum should agglutinate in dilutions of 1 : 50 or greater if it is to be effective at all. More attention should be paid to the differentiation of the various types of meningococci obtainable from patients with meningococcic infections because it is not unreasonable to suppose that the same situation is present here as obtains in the field of pneumococcic infections.

The most effective treatment of this disease is the use of the proper antimeningococcus serum. It is worthy of note that thirty of the thirty-three patient in this series received antimeningococcic serum; one of the three who did not receive serum died. Severe anaphylactic reactions were reported in three cases.[31] The majority of the authors reported prompt improvement after the use of a potent serum. Poor results can usually be accounted for by impotent serum or serum with too low an agglutination titer for the causative organism. Type II and type IV

29. Beaslack, F. W., and others: Cultivation of the Meningococcus Intracellularis (Weichselbaum) from the Blood, J. A. M. A. **70**:684-686 (March 9) 1918.

30. Morgan.[7] Dock.[9]

31. Marlow, F. W.: Meningococcemia: Report of Case with Recovery, J. A. M. A. **92**:619-621 (Feb. 23) 1929. Maxcy.[25a] Seeley.[25b]

meningococci are organisms with a relatively low virulence, in contrast to type I and type III meningococci, and usually cause prolonged and chronic infection. The various commercial serums are made to be especially effective in meningococcic infection caused by the more virulent types, and they vary greatly in their potency for the less virulent types. It is therefore of prime importance that care be exercised in selecting the serum to be used. The amount of serum necessary to bring about a cure varies markedly from case to case, but assuming that a potent serum is being used, quantities from 30 to 500 cc. have been found effective. In case serum proves to be ineffectual, antitoxin should be tried. Vaccine has been employed in a few cases but without striking results. Immunotransfusion [32] seems to be a rational form of therapy, but, again, results are not so gratifying as one would expect. Abscess fixation, nonspecific protein [33] and numerous intravenous antiseptics have all been employed but with only a small measure of success. The recently introduced chemotherapeutic agent sulfanilamide (para-aminobenzenesulfonamide) may prove to be very useful in the treatment of meningococcemia. It should be employed in combination with a potent serum, because there is evidence to support the view that this drug is more effective against certain strains of meningococci than others.[34]

## SUMMARY

Three cases of prolonged meningococcemia are reported, the third being described in detail.

Reports of thirty additional cases collected from the American literature are analyzed and discussed.

Prolonged meningococcemia is a rare disease but should be kept in mind in making a diagnosis in all cases of septicemia in which the essential features are long-standing intermittent fever, cutaneous rash, arthralgia, myalgia, headache and the maintenance of a fair state of health.

An attempt should always be made to differentiate between prolonged meningococcemia and meningococcic endocarditis because of the difference in the prognosis in the two conditions.

The most effective form of treatment is found in the use of the proper antimeningococcus serum in conjunction with sulfanilamide.

32. Edmundson, Frank: Meningococcemia Without Meningeal Symptoms, Hahneman. Monthly **67**:106-109 (Feb.) 1932.

33. Neergaard, Arthur E.: Meningococcus Bacteremia, M. Clin. North America **9**:461-469 (Sept.) 1925.

34. Branham, Sara E., and Rosenthal, Sanford M.: Sulfanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, Pub. Health Rep. **52**:685-695 (May 28) 1937.

# Progress in Internal Medicine

## LIVER AND BILIARY TRACT

A REVIEW FOR 1937

CARL H. GREENE, M.D., PH.D.

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NEW YORK

Previous reviews of the literature dealing with diseases of the liver and biliary tract [1] have made no special reference to textbooks and monographs dealing with the general subject of disease of the liver. At present this policy is abandoned to report the appearance during 1937 of the new textbook on hepatic disease by Eppinger.[2] The book has been divided into two sections—general and special pathology, and the subject has been discussed in truly encyclopedic fashion. For the greater part the views expressed are those generally current, though these have been presented in the light of the author's personal experience in both the experimental laboratory and the medical clinic. This point of view has stressed the work of the German laboratories, but other important contributions have not been overlooked. This volume of 800 pages therefore will take its place as one of the standard reference books for advanced students in this field of medicine. Its cost, unfortunately, will prevent its wider use in this country.

No attempt will be made to review the book in detail or to discuss various controversial points. When the greater frequency of diseases of the gallbladder and bile ducts relative to that of hepatic disease is

From the Clinic for the Study of Diseases of the Liver and Biliary Tract of the Department of Medicine and the Department of Surgery, New York Post-Graduate Medical School and Hospital, and the Long Island College Division of the Kings County Hospital, Brooklyn.

1. Greene, C. H.; Bercovitz, Z., and Hanssen, E. C.: Liver and Biliary Tract: Review of the Literature of 1933 and 1934, Arch. Int. Med. **55**:681 (April) 1935. Greene, C. H.: Liver and Biliary Tract: A Review of Certain Recent Contributions, ibid. **57**:1039 (May) 1936. Greene, C. H.; Handelsman, M. B., and Babey, A. M.: Liver and Biliary Tract: A Review for 1936, ibid. **59**:724 (April) 1937.

2. Eppinger, H.: Die Leberkrankheiten: Allgemeine und spezielle Pathologie und Therapie der Leber, Vienna, Julius Springer, 1937.

considered, it is perhaps unfortunate that the former diseases were not given a proportionate emphasis. Some of this was unavoidable, for while the book was published in 1937, the mechanical aspects of book making consume much time. No references to the American literature later than 1934 were noted, and as pointed out in these reviews, many important contributions have been reported in the past four years.

## PIGMENT METABOLISM IN RELATION TO JAUNDICE AND HEPATIC DISEASE

*Bilirubin.*—Jaundice of itself is evidence of disturbance in the formation or in the excretion of bile. The value of the determination of the bile pigment content of the blood serum (1) in revealing the presence of latent icterus, (2) as an index of the degree of retention of pigment and (3) as a measure of the changes during the course of the disease has been thoroughly demonstrated. Various methods have been used for this study of the pigment in the serum, the simplest and most popular being the icterus index and the quantitative van den Bergh reaction.

It is generally accepted that bilirubin is formed by the decomposition of hemoglobin. This destruction of blood pigment takes place primarily in the cells of the reticuloendothelial system rather than in the parenchymal cells of the liver. The Kupffer cells of the liver, which are part of the reticuloendothelial system, thus take part in the formation of bile pigment, but considerable quantities of bilirubin are formed in the spleen and bone marrow as well. It has been argued that the liver acts as an excretory organ with respect to bilirubin, just as the kidney does with respect to urea. This analogy may not be entirely accurate, for the bile pigment apparently is modified slightly during the process of excretion. The pigment which is normally present in the blood serum in small amount gives an indirect van den Bergh reaction. After the bilirubin has passed through the hepatic cells and entered the bile, the van den Bergh reaction becomes direct. There has been a great deal of controversy regarding the reason for this change in the character of the bilirubin. Some investigators insist that there are distinct chemical differences, and Harrison [3] suggested the use of the terms hemobilirubin and cholebilirubin to designate the two types of pigment. Regardless of the final explanation of the two types of van den Bergh reaction, the finding of an indirect reaction in the presence of clinical jaundice empirically but conclusively demonstrates that the jaundice is hemolytic in origin. The so-called delayed

3. Harrison, G. A.: Chemical Methods in Clinical Medicine: Their Application and Interpretation, with the Technique of the Simple Tests, London, J. & A. Churchill, 1930.

and diphasic types of reaction apparently are quantitative modifications of the direct reaction and are valueless for the differentiation of hepatogenous from obstructive types of jaundice.

Hemobilirubin is present in normal blood serum and is increased in amount in cases of hemolytic jaundice. It gives the indirect van den Bergh reaction and is readily extracted by chloroform. The cholebilirubin present in bile and in the blood serum in cases of hepatic or of obstructive jaundice gives the direct van den Bergh reaction and is not extracted by chloroform. Hemobilirubin has been described as bound by protein and therefore nondialyzable, in contrast to cholebilirubin, which is free and dialyzable. We have not found this to be a satisfactory method of separation of the two fractions, and similar results have been reported by Gregory and Andersch.[4] The differences in solubility in chloroform permit an apparent separation of the two types of pigment in the serum. Varela and Esculies,[5] Kerppola,[6] and Bengolea, Velasco-Suárez and Raices[7] have reported quantitative studies of the two types of bilirubin in the blood of jaundiced patients. In jaundice there may be an increase in the amount of both the water-soluble and the chloroform-soluble bilirubin in the serum, but the relative proportion of the two is not constant; they seem to vary independently (fig. 1).

If further studies substantiate the separate identity of the two forms of bilirubin and the validity of this method of separation, it may then be possible to assay the relative importance of the two factors, that is, icterus by retention and icterus by resorption, which are the basis of the classification of jaundice proposed by Rich.[8] The results indicate that in most cases of jaundice the hemobilirubin fraction is increased with the appearance of cholebilirubin in the serum and so suggest that hemolytic processes play a larger role in the pathogenesis of jaundice than is usually accepted.

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4. Gregory, R. L., and Andersch, M.: The Filterability of Bilirubin in Obstructive Jaundice, J. Lab. & Clin. Med. **22**:1111, 1937.

5. Varela, B., and Esculies, J.: Nouvelle méthode pour la séparation et le dosage des deux bilirubines (directes et indirectes) du sérum sanguin, Compt. rend. Soc. de biol. **107**:884, 1931. Varela, B.; Recorte, P., and Esculies, J.: Méthode simplifiée pour la séparation et le dosage isolé des deux bilirubines, directe et indirecte, du sérum sanguin dans les ictères, ibid. **108**:1009, 1931.

6. Kerppola, W.: Extraction Method for the Quantitative Determination of Bilirubin in Different Body-Fluids, Acta med. Scandinav., 1932, supp. 50, pp. 277-280.

7. Bengolea, A. J.; Velasco-Suárez, C., and Raices, A. E.: El dosaje de la bilirubina directa et indirecta en el suero sanguineo: Su importancia en cirurgía hepato bilar, Prensa méd. argent. **23**:85, 1936.

8. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338, 1930.

*Urobilin and Urobilinogen.*—The early investigations of Friedrich von Müller [9] first established the importance of urobilinuria as evidence of a disturbance in hepatic function. The clinical value of qualitative or semiquantitative tests for urobilin as urobilinogen in the urine and stools has been summarized in such reports as those of Wilbur and Addis,[10] Wallace and Diamond,[11] White [12] and Eppinger,[13] and

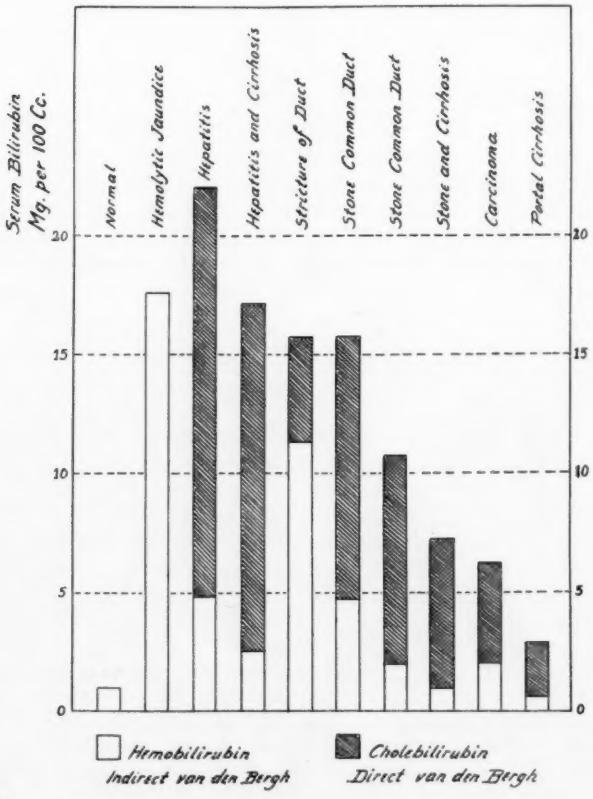


Fig. 1.—The distribution of the two types of bilirubin in the serum in an illustrative series of cases of jaundice (authors' data).

9. von Müller, F.: Ueber Ikterus, Jahresb. d. schles. Gesellsch. f. vaterl. Kult. **70**:1, 1893.

10. Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

*(Footnotes continued on next page)*

many otherwise controversial questions have been settled by the experimental studies of Elman and McMaster.[14] These various studies have demonstrated that urobilinogen normally is formed in the intestine by the bacterial decomposition of the bile pigments. Some of the urobilinogen is absorbed and is carried by the portal blood stream to the liver. A portion possibly may be used in the synthesis of hemoglobin, but the major part is excreted in the bile. If bile is excluded from the intestine, either because of the presence of complete biliary obstruction or because of a biliary fistula, the formation of urobilinogen ceases, and this pigment disappears from the bile, stool and urine. The liver normally removes nearly all the urobilinogen from the portal blood, and only small amounts escape into the systemic circulation to appear in the urine.

The reserve capacity of the liver for the excretion of urobilinogen is slight, and slight degrees of hepatic injury or damage therefore suffice to permit the escape of urobilinogen into the general circulation and its appearance in the urine. This accounts for the frequency of urobilinogenuria in cases of jaundice due to hepatitis or to stones in which the obstruction to the common duct is not complete. Positive results of tests are also the rule in portal cirrhosis in which hepatic damage is present and in which the presence of collateral venous channels makes it possible for urobilinogen to pass from the portal to the systemic circulation without passing through the liver.

Urobilinogenuria also is present in blood dyscrasias, such as hemolytic jaundice or pernicious anemia, and in pneumonia, pulmonary infarction, hemorrhage and other conditions in which an increased destruction of hemoglobin and the excretion of an increased amount of pigment in the bile occurs. More urobilinogen is formed in the intestine, and the consequent flooding of the liver is assumed to explain the urobilinogenuria. Whether all the urobilinogenuria in such cases can be explained on this basis or whether an additional element of

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11. Wallace, G. B., and Diamond, J. S.: Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

12. White, F. W.: The Galactose-Tolerance and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice, Tr. A. Am. Physicians **50**:111, 1935; Am. J. Digest. Dis. & Nutrition **4**:315, 1937.

13. Eppinger, H.: Die hepato-lienalen Erkrankungen, Berlin, Julius Springer, 1920.

14. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. The Quantitative Determination of Urobilin, J. Exper. Med. **41**: 503, 1925; II. Derivation of Urobilin; Relation of Bile to the Presence of Urobilin in the Body, ibid. **41**:513, 1925; III. Absorption of Pigments of Biliary Derivation from the Intestine, ibid. **41**:719, 1925; IV. Urobilin and the Damaged Liver, ibid. **42**:99, 1925; V. The Relation Between Urobilin and Conditions Involving Increased Red Cell Destruction, ibid. **42**:619, 1925; VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, ibid. **43**:753, 1926.

hepatic damage, perhaps produced by the associated anemia, must be assumed is still open to question.

In the great majority of cases the presence of urobilinogenuria is evidence of the presence of bile in the intestinal tract. Even with complete biliary obstruction, traces of urobilinogen may be formed from bile-stained epithelial cells in the intestine. Infection of the biliary tract may also give rise to a local formation of urobilinogen. Such cases are infrequent, and these modes of formation of urobilinogen are of little clinical significance.

The early investigation of urobilinuria demonstrated the fluctuations observed in the study of casual specimens and emphasized the importance of quantitative determinations of the daily excretion in the urine

*The Daily Excretion of Urobilinogen in Health and in Disease (Watson)*

| | Number of Cases | Urobilin Excretion Mg. per Day | |
|---|---|---|---|
| | | Urine | Feces |
| Normal condition | 26 | 0-4 | 40-280 |
| Chronic infection | 5 | 0-1 | 0-100 |
| Febrile condition | 11 | 0-38 | 100-300 |
| Obstructive Jaundice | | | |
| Uncomplicated cholelithiasis | 21 | 0-6 | 10-250 |
| Stones with complications | 20 | 4-50 | 10-250 |
| Neoplastic disease | 18 | 0-0.3 | 0-5 |
| Diffuse hepatitis | | | |
| Acute catarrhal jaundice | 11 | 4-200 | 10-300 |
| Diffuse hepatitis with jaundice | 10 | 4-100 | 8-200 |
| Diffuse hepatitis or cirrhosis with blood destruction | 7 | 20-200 | 300-1,200 |
| Diffuse hepatitis or cirrhosis without jaundice | 8 | 4-100 | 50-135 |
| Congestive heart failure with jaundice and ascites | 11 | 0-50 | 30-260 |
| Carcinoma of the liver without jaundice | 6 | 0-25 | |
| Familial or congenital hemolytic jaundice | 10 | 1-10 | 300-1,800 |
| Acquired hemolytic jaundice | 3 | 10-300 | 300-2,500 |

and stool. Moderately satisfactory methods for such study were devised by Terwen [15] and more recently by Watson.[16] The latter made a comprehensive study of the urobilinogen in the urine and stool both of normal subjects and of patients with disease of the liver and biliary tract.

Watson [17] studied 26 normal subjects and found that the urobilinogen excreted in the urine varies from 0 to 4 mg. per day, usually from

15. Terwen, A. J. L.: Ueber ein neues Verfahren zur quantitativen Urobilin-Bestimmung im Harn und Stuhl, Deutsches Arch. f. klin. Med. **149**:72, 1925.

16. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458, 1936.

17. Watson, C. J.: Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937; III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, ibid. **59**:206 (Feb.) 1937.

0.5 to 2 mg. The urobilinogen content of the feces varies from 40 to 280 mg. Mild infection, inanition or inactivity, uncomplicated by jaundice or anemia, tends to lower the excretion of urobilinogen in the feces. Fever of any considerable degree tends to increase the amount of urobilinogen in the feces, but fever alone without jaundice does not increase the degree of urobilinuria.

One hundred and thirty-five patients with jaundice or hepatic disease were studied by Watson.[18] In obstructive jaundice due to cholecystitis or cholelithiasis without complications the excretion of urobilinogen in the urine or in the stool was only slightly increased if at all over the normal. Relief of the obstruction with subsidence of the jaundice, apparently was accompanied temporarily by a marked increase in the excretion of urobilinogen, particularly that in the urine. In contrast to the findings in obstruction due to calculus, which rarely was complete, were those in carcinomatous obstruction. The degree of obstruction in the latter case usually was complete, and this was signalled by the almost complete disappearance of urobilinogen from both urine and stool.

In cases of acute catarrhal jaundice there was a normal excretion of urobilinogen in the stool, but the amount excreted in the urine regularly was increased over the amount found in cases of uncomplicated jaundice with stone. Similar findings were observed in cases of chronic hepatitis or cirrhosis.

Cases of chronic hepatitis or cirrhosis which was accompanied by an increased destruction of blood were characterized by the presence of an increased amount of urobilinogen in the urine, but the increase in the output of urobilinogen in the stool was especially marked.

The content of urobilinogen in the feces usually was increased to a marked degree in cases of hemolytic jaundice. In such cases splenectomy resulted in a rapid decrease. The urobilinogen content of the urine, however, was only moderately increased and could not be correlated with the increased destruction of blood. Watson therefore concluded that the urobilinuria seen in hemolytic types of jaundice was not due to flooding or overloading of the liver with urobilinogen but was evidence of functional disturbance in the liver.

These data reported by Watson confirm and extend the previously reported views by showing that the presence of urobilinogen in feces or urine is dependent on the passage of bile through the common duct into the intestine. Transient obstruction may occur from stones or acute hepatitis, but persistent complete obstruction nearly always is

18. Watson, C. J.: The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**: 698 (May) 1931. Watson.[17]

due to neoplasm. The amount of urobilinogen in the stool appears to vary with the rate of destruction of blood and presumably, therefore, with the excretion of bile pigment. The excretion of urobilinogen in the urine is a measure of hepatic insufficiency which, however, may be variously produced. It is most frequent and marked in the presence of diffuse hepatic disease. It is not present in cases of cholelithiasis unless there are complications, such as infection or anemia. In hemolytic jaundice the urobilinuria when present was a measure of hepatic dysfunction from anemia or other causes rather than a "flooding" of the liver as a result of the increased destruction of blood.

The collection of specimens and the quantitative determination of the daily excretion of urobilinogen in the urine and stools constitute a laborious procedure, but Watson has amply demonstrated its great diagnostic significance.

*Porphyrins and Porphyrin Metabolism.*—The urine and stool contain not only bile pigments and their derivatives but another series of pigments, the porphyrins. These are of great biologic interest, for, as described in a recent review of this subject by Hans Fischer,[19] the respiratory pigments are porphyrin compounds. The hemoglobin of the red blood corpuscles and the myoglobin of muscles are compounds composed of a porphyrin, iron and a protein. The chlorophyll of green plants is a porphyrin-magnesium compound. The brown pigment of egg shells,[20] the pigment (turacin) [21] in the feathers of one species of South African bird, the chlorocruorin [22] found in rare species of worms and the cytochrome C [23] found in yeast cells [24] and in many species of animals and plants are all porphyrin compounds.

The chemical structure of the porphyrins has been elucidated as a result largely of the work of Hans Fischer and his pupils.[19] They have shown that porphyrins are composed of four pyrrole nuclei united by four methene bridges to form the porphin ring. In the naturally

19. Fischer, H., and Orth, H.: Die Chemie des Pyrrols, Leipzig, Akademische Verlagsgesellschaft m. b. H., 1937, vol. 2.

20. Fischer, H., and Kögl, F.: Zur Kenntnis der natürlichen Porphyrine: IV. Ueber das Ooporphyrin, Ztschr. f. physiol. Chem. **131**:241, 1923. Fischer, H., and Lindner, F.: XIV. Ueber Ooporphyrin und seine Ueberführung in den Ester des Hämins, ibid. **142**:141, 1925.

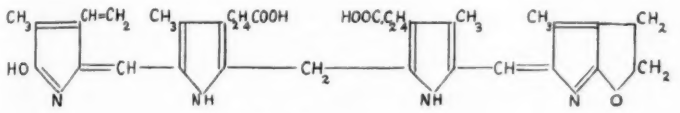
21. Fischer, H., and Hilger, J.: Zur Kenntnis der natürlichen Porphyrine: Ueber das Vorkommen von Uroporphyrin in den Turakovögeln und den Nachweis von Koproporphyrin in der Hefe, Ztschr. f. physiol. Chem. **138**:59, 1924.

22. Fischer, H., and von Seemann, C.: Die Konstitution des Spirographishämins, Ztschr. f. physiol. Chem. **242**:133, 1936.

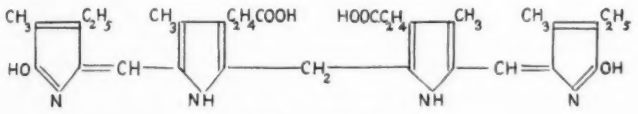
23. Zeile, K., and Reuter, F.: Ueber Cytochrom C, Ztschr. f. physiol. Chem. **221**:101, 1933.

24. Fischer, H., and Hilmer, H.: Ueber Koproporphyrin-Synthese durch Hefe und ihre Beeinflussung, Ztschr. f. physiol. Chem. **153**:167, 1926.

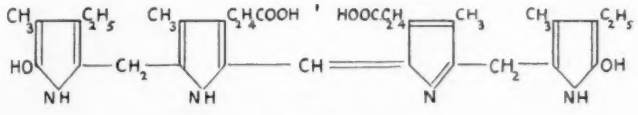
occurring porphyrins, various chemical groups have been substituted for the hydrogen atoms in the periphery of the porphin nucleus. By different arrangements of the substituting groups, a number of isomeric chemical compounds are possible. When the eight hydrogen atoms of the porphin nucleus are substituted, with four methyl and four



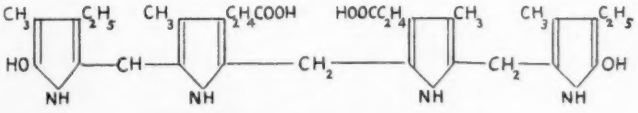
BILIRUBIN



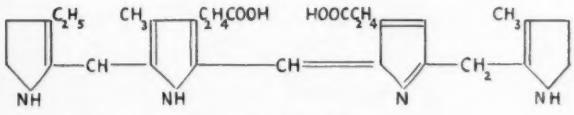
MESOBILIRUBIN



UROBILIN



MESOBILIRUBINOGEN - UROBILINOGEN



STERCOBILIN

Fig. 2.—The structural formulas of bilirubin, urobilinogen and related compounds (after Fischer).

ethyl groups, four isomeric etioporphyrins (types I to IV) are formed. They differ only in the arrangement of the substituent groups. The etioporphyrins do not occur naturally but are of importance as reference types, for the naturally occurring porphyrins may be classified as of similar construction to etioporphyrin of either type I or type III.

The respiratory pigments, hemoglobin,[19] myoglobin,[25] cytochrome C,[23] chlorophyll and catalase,[26] are all compounds of type III porphyrin. The chemical formulas of some of these compounds are given in figures 2 to 4.

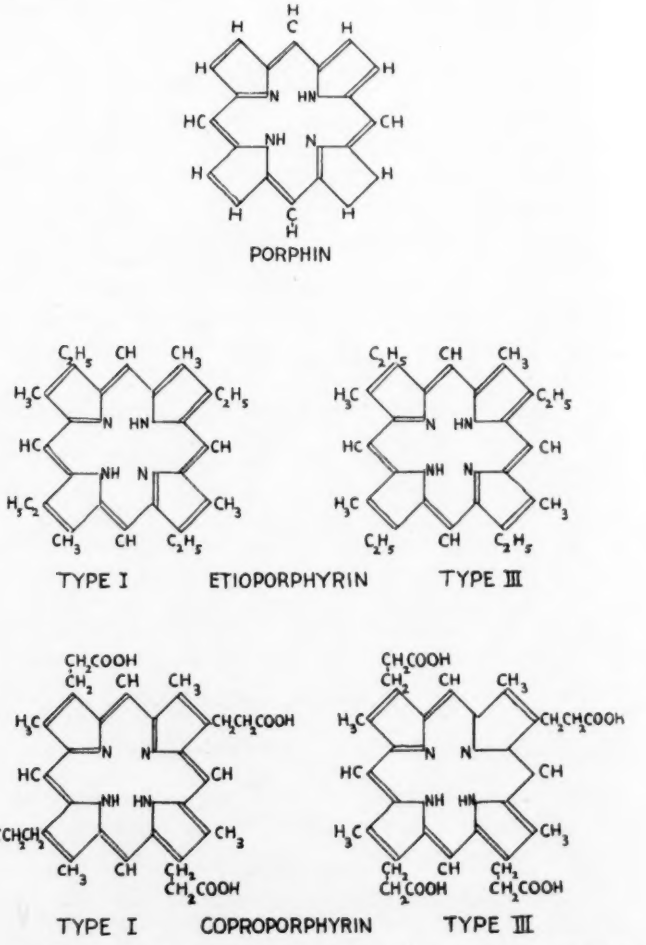



Fig. 3.—The structural formulas of porphin and related compounds (after Fischer).

25. Schönheimer, R.: Ueber den roten Farbstoff der Herz- und Skelettmuskulatur, Ztschr. f. physiol. Chem. **180**:144, 1929.

26. Stern, K. G.: The Constitution of the Prosthetic Group of Catalase, J. Biol. Chem. **112**:661, 1936.

The early reports of Garrod [27] and Günther [28] demonstrated the occurrence of clinical cases of porphyria, and Garrod emphasized that such cases represented a rare type of constitutional anomaly of pigment metabolism. Mason, Courville and Ziskind [29] summarized this literature and reported that congenital porphyria has been recorded in 27 cases and acute idiopathic porphyria in 48 cases. They also reported that about 100 cases of acute toxic porphyria have been recorded. Most

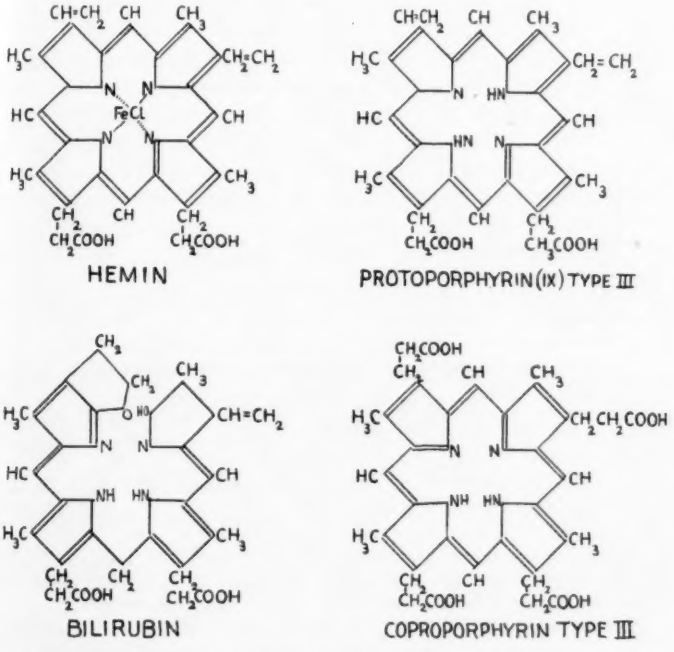



Fig. 4.—The structural formulas of various derivatives of type III porphyrin (after Fischer).

of these cases followed the long-continued abuse of sulfonmethane or sulfonethylmethane. Porphyrin metabolism has been summarized in

27. Garrod, A. E.: Hematoporphyrin in Normal Urine, J. Physiol. **17**:349, 1894; Inborn Errors of Metabolism, ed. 2, London, Humphrey Milford, 1923, p. 136.

28. Günther, H.: Die Bedeutung der Hämatoporphyrie in Physiologie und Pathologie, Ergebn. d. allg. Path. u. path. Anat. **20**:609, 1922

29. Mason, V. R.; Courville, C., and Ziskind, E.: The Porphyrins in Human Disease, Medicine **12**:355, 1933.

the reviews of Brugsch,[30] Carrié,[31] Vannotti [32] and others.[33] Porphyria has been shown by Turner [34] to be present in the fox squirrel, in which the bones and urine normally are stained red by porphyrins.

The excretion of porphyrins, however, is not limited to cases of porphyria, for small amounts are excreted in the urine and stool both of normal persons and of patients suffering from a variety of pathologic conditions.[35] The amount excreted usually is too small to produce clinical symptoms, though Beckh, Ellinger and Spies [36] have reported that in pellagra the excretion of porphyrin bears a rough relation to the intensity of the cutaneous lesions, and they have pointed out the similarity between the cutaneous symptoms of congenital porphyrinuria and those of pellagra. An increased excretion of porphyrins does not always produce cutaneous symptoms, for most patients with acute or chronic porphyrinuria do not manifest this symptom.[37] The porphyrins in the urine and stool of normal persons and of patients, including those with acute, chronic or congenital porphyria, consist preponderantly of coproporphyrin type I, with traces of protoporphyrin type III and deuteroporphyrin type III. Uroporphyrins of types I and

30. Brugsch, J. T.: Die sekundären Störungen des Porphyrinstoffwechsels, Ergebn. d. inn. Med. u. Kinderh. **51**:86, 1936.

31. Carrié, C.: Die Porphyrine, Leipzig, Georg Thieme, 1936.

32. Vannotti, A.: Porphyrin und Porphyrinkrankheiten, Berlin, Julius Springer, 1937.

33. Kämmerer, H.: Biologie und Klinik der Porphyrine, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **45**:28, 1933. Fischer, H.: Ueber Hämin und Porphyrine, ibid. **45**:7, 1933.

34. Turner, W.: Studies on Porphyria: Observations on the Fox Squirrel, J. Biol. Chem. **118**:519, 1937.

35. (*a*) Fink, H., and Hoerburger, W.: Isolierung von kristallisiertem Koproporphyrin I aus normalen menschlichen Urin, Naturwissenschaften **18**: 292, 1934. (*b*) Watson, C. J.: Concerning the Naturally Occurring Porphyrins: I. Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, J. Clin. Investigation **14**:106, 1935; II. The Isolation of a Hitherto Undescribed Porphyrin Occurring with an Increased Amount of Coproporphyrin I in the Feces in a Case of Familial Hemolytic Jaundice, ibid. **14**:110, 1935; III. Isolation of Coproporphyrin I from the Feces of Untreated Cases of Pernicious Anemia, ibid. **14**:116, 1935; IV. Urinary Porphyrins in Lead Poisoning as Contrasted with that Excreted Normally and in Other Diseases, ibid. **15**:327, 1936; V. Porphyrins of the Feces, ibid. **16**:383, 1937. (*c*) Dobriner, K.: Urinary Porphyrins in Disease, J. Biol. Chem. **113**:1, 1936; Porphyrin Excretion in the Feces in Normal and in Pathological Conditions, ibid. **120**:115, 1937. (*d*) Vigliani, E. C., and Libowitzky, H.: Ueber Porphyrine im Harn und im Kot, Klin. Wchnschr. **16**: 1243, 1937.

36. Beckh, W.; Ellinger, P., and Spies, T. D.: Porphyrinuria in Pellagra, Quart. J. Med. **6**:305, 1937.

37. Waldenström, J.: Studien über Porphyrie, Acta med. Scandinav., 1937, supp. 82, pp. 1-254.

III have also been recovered in cases of acute, chronic and congenital porphyria. Porphyrins of type I thus constitute the usual type found both normally and in the majority of pathologic conditions.

Coproporphyrin type III has been reported in the excreta in certain cases of lead poisoning,[38] in cases of aplastic anemia [39] and in cases of atrophic cirrhosis, pigment cirrhosis and melanocarcinoma of the liver.[40] The perfusion experiments of van den Bergh, Grotepass and Revers [41] have demonstrated that the surviving liver is capable of converting protoporphyrin into coproporphyrin. Because of the hepatic damage in these cases it is possible that some of the protoporphyrin formed by the destruction of hemoglobin escapes conversion into bilirubin and may be converted into coproporphyrin type III. The evidence today, however, is too fragmentary for this explanation to be accepted as more than a hypothesis.

Such a hypothesis, however, will not explain the production of porphyrin of type I in nearly all the cases studied. Porphyrins of types I and III cannot be converted the one into the other by chemical means without breakdown to simple pyrroles and resynthesis.[42] It is extremely unlikely that the body can convert porphyrin of one type into that of another, and Fischer [42] has emphasized the dual nature of the porphyrins in consequence. The studies of Dobriner [35c] and of Watson [35b] in particular have indicated further that coproporphyrin is chiefly if not entirely endogenous. The amounts excreted were greatest in cases of hemolytic jaundice and pernicious anemia or after hemorrhage or therapeutic hemolysis in a case of polycythaemia vera in which the regeneration and bone marrow activity were greatest, and they were least in a case of anemia associated with destruction of bone marrow.[43]

38. Grotepass, W.: Zur Kenntnis des im Harn auftretenden Porphyrins bei Bleivergiftung, Ztschr. f. physiol. Chem. **205**:193, 1932. Franke, K., and Litzner, G.: Quantitative Determination of Porphyrin in Urine as an Aid in Early Recognition of Lead Poisoning, Ztschr. f. klin. Med. **129**:115, 1935. Roth, E.: Lead Poisoning and Porphyria, ibid. **129**:123, 1935. Watson,[35b] 1936.

39. Dobriner, K., and Rhoads, C. P.: The Excretion of Porphyrin in Refractory and Aplastic Anemia, J. Clin. Investigation **17**:125, 1938.

40. Watson, C. J.: The Porphyrins and Their Relation to Disease: Porphyria, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, London, Oxford University Press, 1938, vol. 4, pt. 1, p. 228 (1). Dobriner.[35c]

41. van den Bergh, A. A. H.; Grotepass, W., and Revers, F. E.: Beitrag über das Porphyrin in Blut und Galle, Klin. Wchnschr. **11**:1534, 1932.

42. Fischer, H.: Ueber Porphyrine und ihre Synthesen, Ber. d. deutsch. chem. Gesellsch. **2**:2611, 1927; Ueber Hämin und Porphyrine, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **45**:7, 1933. Fischer and Orth.[19]

43. Dobriner, K.; Strain, W. H., and Localio, S. A.: (*a*) I. Quantitative Measurement of Coproporphyrin and Total Coproporphyrin I Excretion in Normals, Proc. Soc. Exper. Biol. & Med. **36**:752, 1937; (*b*) II. Coproporphyrin I Metabolism and Hematopoietic Activity, ibid. **36**:755, 1937.

The studies of Dobriner and his collaborators [44] have further shown a parallelism between the rates of excretion of coproporphyrin type I and the rates of excretion of urobilinogen. These various investigations led Dobriner, Localio and Strain [45] to suggest that the synthesis of porphyrins in vivo is directed to the formation of large amounts of type III porphyrin and a small amount of type I porphyrin as products of the same synthesis. Physiologically there is a direct proportion between the construction of the two types of porphyrin. Type III porphyrin is used in the formation of the respiratory pigments, and type I porphyrin is excreted mainly as coproporphyrin I. Since an increase or decrease in the synthesis of hemoglobin is paralleled by the formation and excretion of type I porphyrin, the excretion of coproporphyrin I has been used by Dobriner, Strain and Localio [43] and by Dobriner and Rhoads [44b] as an index of hematopoietic activity both in normal persons and in persons in whom there is an orderly increase or decrease in hematopoiesis. Borst and Königsdorffer [46] and Turner [34] have pointed out that there is formation of uroporphyrin I associated with the fetal megaloblastic type of erythropoiesis. Protoporphyrin has been found in marrow erythroblasts [46] and in human reticulocytes.[47] Watson [35b] also found an increased excretion of protoporphyrin in the same instances in which the feces contained increased amounts of coproporphyrins. This protoporphyrin was not finally identified but showed differences in behavior which suggested that it was not the same as protoporphyrin type III derived from hemoglobin. This evidence is in accord with the studies of Dobriner and his co-workers in linking the production of coproporphyrin I with erythropoietic activity.

The results thus far have shown that the liver plays an important role in the excretion and possibly in the metabolism of the porphyrins. In most instances the excreted porphyrin is type I coproporphyrin.[48] However, in some diseases type III coproporphyrin has been recovered.[49]

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44. (*a*) Dobriner, K.: Excretion of Porphyrin by Dogs, Proc. Soc. Exper. Biol. & Med. **36**:757, 1937. (*b*) Dobriner, K., and Rhoads, C. P.: The Excretion of Coproporphyrin I Following Hemorrhage in Dogs, J. Clin. Investigation **17**: 105, 1938; Metabolism of Blood Pigments in Pernicious Anemia, ibid. **17**:95, 1938. (*c*) Dobriner, Strain and Localio.[43]

45. Dobriner, K.; Localio, S. A., and Strain, W. H.: A Study of the Porphyrins Excreted in Congenital Porphyrinuria, J. Biol. Chem. **114**:xxvi, 1936. van den Bergh, Grotepass and Revers.[41] Fischer.[42] Footnote 44.

46. Borst, M., and Königsdorffer, H.: Untersuchungen über Porphyrie, Leipzig, S. Hirzel, 1929.

47. Watson, C. J., and Clarke, W.: The Occurrence of Protoporphyrin in the Reticulocytes, Proc. Soc. Exper. Biol. & Med. **36**:65, 1937.

48. Watson.[35b] Dobriner.[35c]

49. Vigliani, E., and Angeleri, C.: Ueber das im Plasma Bleikranker vorkommende Porphyrin, Klin. Wchnschr. **15**:700, 1936. Vigilani, E., and Waldenström, J.: Die Porphyrine beim Saturnismus, Deutsches Arch. f. klin. Med. **180**:182, 1937. Dobriner. [35c]

Garrod [27] and Günther [28] in their early work noted an increased urinary excretion of porphyrin in cases of hepatic disease. Quantitative data on urinary porphyrin have been recorded by Thiel,[50] Boas [51] and Lageder.[52] Brugsch [53] measured the urinary output of coproporphyrin before and after a meal of liver and concluded that an increase in the urinary coproporphyrin content following such a meal is a sensitive indicator of hepatic insufficiency. Tropp and Penew [54] have recently published more complete data on the relation of the porphyrins to hepatic damage, as have also Kämmerer and Meyer.[55] All these studies indicate that an increased urinary output of porphyrin is an early indication of hepatic insufficiency.

The observed increase in the urinary output of coproporphyrin is perhaps due to two factors—an increased production and an inability to excrete porphyrins into the bile on the part of the damaged liver. If so, there is a marked similarity between the pathway of excretion of the porphyrins and that of urobilinogen and bile pigments.

The entire subject is in its infancy. All authors, with the exception of Brugsch, have determined only the urinary output of coproporphyrin. The studies of fecal porphyrin conducted by Brugsch, however, were inconclusive, since the various porphyrins excreted were not separated. With the newer methods now available it appears that accurate determinations of the urinary and fecal output of coproporphyrin can be made. Studies utilizing these methods to determine the ratio between the urinary and the fecal output of coproporphyrin, as suggested by Brugsch, will yield valuable information. The studies thus far indicate that in hepatic disease there is a shift of the ratio between the urinary output and the fecal output of coproporphyrin in favor of the urinary porphyrins.

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50. Thiel, W., and Kämmerer, H.: Quantitative Porphyrinmessungen bei verschiedenen Krankheiten, Verhandl. d. deutsch. Gesellsch f. inn. Med. **45**:81, 1933.

51. Boas, J.: Ueber das Vorkommen von Protoporphyrin im Harn, Klin. Wchnschr. **12**:589, 1933.

52. Lageder, K.: Klinische Porphyrinuntersuchungen mit einer quantitativen spectroskopischen Methode, Arch. f. Verdauungskr. **56**:237, 1934.

53. Brugsch, J. T.: Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen, Ztschr. f. d. ges. exper. Med. **95**:471, 482 and 493, 1935. Keys, A., and Brugsch, J. T.: Porphyrins and Porphyrinemia, Am. J. Digest. Dis. & Nutrition **5**:49, 1938.

54. Tropp, C., and Penew, L.: Quantitative Clinical Study of the Urinary Porphyrin in Hepatic Cirrhosis, Hepatopathies Exclusive of Cirrhosis, Tuberculosis and Other Diseases: Improved Technic of Determining the Porphyrins, Deutsches Arch. f. klin. Med. **180**:423, 1937.

55. Kämmerer, H., and Meyer, W. K.: Ueber abdominale idiopathische Porphyrie, Deutsches Arch. f. klin. Med. **179**:392, 1936.

PHOSPHATASE IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

The various tests of hepatic function which have been recommended as of value in the differential diagnosis of jaundice are legion. The status of many of them has been discussed in previous articles of this series or in such articles as the recent one of Snell and Magath,[56] in which most of the generally accepted tests have been discussed. Much controversy has arisen over the diagnostic significance of the phosphatase values of the serum in jaundice.[57] Roberts [58] first reported that this value is increased in obstructive jaundice. He obtained normal values in cases of hepatitis or catarrhal jaundice and so suggested the use of this test in making a differential diagnosis. This view has been substantiated by the reports of Armstrong;[58a] Rothman, Meranze and Meranze,[59] and Flood, Gutman and Gutman.[60] The elevation of the phosphatase content in cases of obstructive jaundice is accepted, as is the finding of normal values in cases of hemolytic jaundice. Such cases have been reported by Roberts;[58] Greene, Shattuck and Kaplowitz [61] Herbert;[62] Anderson,[63] and Flood, Gutman and Gutman.[60]

The majority of investigators who have studied the phosphatase content in cases of hepatitis or of catarrhal jaundice have reported variable results. Normal values frequently are obtained. Elevated values are met with sufficient frequency markedly to limit the diagnostic value of this test, if not to render it valueless.[64]

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56. Snell, A. M., and Magath, T. B.: The Use and Interpretation of Tests for Liver Function: A Clinical Review, J. A. M. A. **110**:167 (Jan. 15) 1938.

57. Cantarow, A.: Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, Internat. Clin. **1**:230, 1936. Morris, N., and Peden, O. D.: Plasma Phosphatase in Disease: A Review, Quart. J. Med. **6**:211, 1937.

58. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930; Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933.

58a. Armstrong, A. R.; King, E. J., and Harris, R. I.: Phosphatase in Obstructive Jaundice, Canad. M. A. J. **31**:14, 1934.

59. Rothman, M. M.: Meranze, D. R., and Meranze, T.: Blood Phosphatase as an Aid in Differential Diagnosis of Jaundice, Am. J. M. Sc. **192**:526, 1936.

60. Flood, C. A.; Gutman, E. B., and Gutman, A. B.: Phosphatase Activity, Inorganic Phosphorus and Calcium of Serum in Disease of the Liver and Biliary Tract: A Study of One Hundred and Twenty-Three Cases, Arch. Int. Med. **59**: 981 (June) 1937.

61. Greene, C. H.; Shattuck, H. F., and Kaplowitz, L.: The Phosphatase Content of the Blood Serum in Jaundice, J. Clin. Investigation **13**:1079, 1934.

62. Herbert, F. K.: The Plasma Phosphatase in the Various Types of Jaundice, Brit. J. Exper. Path. **16**:365, 1935.

63. Anderson, R. G.: The Plasma Phosphatase in Jaundice, St. Barth. Hosp. Rep. **68**:221, 1935.

64. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: IV. Serum Phosphatase of Non-Osseous Origin; Significance of the Variations of Serum Phospha-

*(Footnote continued on next page)*

The results of experimental studies likewise have been variable. The phosphatase content is increased in experimental obstructive jaundice in dogs [65] but not in cats.[66] Toxic injury to the liver in dogs by a variety of methods has been shown by Hartman and Schelling [67] and by Armstrong and King [68] to produce an increase. A similar increase has been observed in cases of complete biliary fistula. No satisfactory single explanation of these various and apparently contradictory clinical and experimental observations has been propounded thus far. Thannhauser and his collaborators [69] have reported recently an extensive series of observations which offer an alternative explanation and do much to clarify the situation.

Bodansky [70] observed that there was a paradoxic increase in the phosphatase content of serum on standing. Thannhauser found that cevitamic acid was an intense activator of serum phosphatase. Normal subjects responded with an increase of from 100 to 134 units. Patients with hepatic disease or experimental animals with high initial values did not show such rises after the addition of cevitamic acid. He con-

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tase in Jaundice, Proc. Soc. Exper. Biol. & Med. **31**:107, 1933. Austoni, B., and Caggi, G.: La phosphatase du plasma dans differentes affections, Presse méd. **42**:1594, 1934. Fiessinger, N., and Boyer, F.: La phosphatase plasmatique en pathologie hepatique, Rev. méd.-chir. d. mal. du foie **10**:137, 1935. Cantarow, A., and Nelson, J.: Serum Phosphatase in Jaundice, Arch. Int. Med. **59**:1045 (June) 1937. Greene, Shattuck and Kaplowitz.[61] Herbert.[62] Anderson.[63]

65. (*a*) Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: VIII. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, Proc. Soc. Exper. Biol. & Med. **31**:1179, 1934. (*b*) Armstrong, A. R.; King, E. J., and Harris, R. I.: Phosphatase in Obstructive Jaundice, Canad. M. A. J. **31**:14, 1934.

66. Cantarow, A.; Stewart, H. L., and McCool, S. G.: Serum Phosphatase in Cats with Total Bile Stasis, Proc. Soc. Exper. Biol. & Med. **35**:87, 1936.

67. Hartman, F. W., and Schelling, V.: Serum Phosphatase in Experimental Insufficiency of the Liver, Arch. Path. **18**:594 (Oct.) 1934.

68. Armstrong, A. R., and King, E. J.: Serum Phosphatase in Toxic and Hemolytic Jaundice, Canad. M. A. J. **32**:379, 1935.

69. Thannhauser, S. J.; Reichel, M., and Grattan, J. F.: Studies on Serum Phosphatase Activity: I. Ascorbic Acid Activation on Serum Phosphatase, J. Biol. Chem. **121**:697, 1937. Thannhauser, S. J.; Reichel, M.; Grattan, J. F., and Maddock, S. J.: II. The Effect of Experimental Total Biliary Obstruction on the Serum Phosphatase Activation in Dogs and Cats, ibid. **121**:709, 1937; III. The Effect of Complete Biliary Fistula on Phosphatase Activity in Serum and Bile, ibid. **121**:715, 1937; IV. The Deactivating Effect of Thiol Compounds and Bile Acids on Serum Phosphatase in Vitro and in Vivo, ibid. **121**:720, 1937; V. Studies Concerning Increased Serum Phosphatase Values in Disease, ibid. **121**:727, 1937. Maddock, S.; Thannhauser, S. F.; Reichel, M., and Grattan, J. F.: A New Conception of Serum Phosphatase: Review of Experimental Work, New England J. Med. **218**:166, 1938.

70. Bodansky, A.: Paradoxical Increase of Phosphatase Activity in Preserved Serum, Proc. Soc. Exper. Biol. & Med. **29**:1292, 1932.

cluded that the high values previously reported are to be explained as due to an increased activation of phosphatase and not to an increase in the total amount of enzyme present in the serum. The exact nature of this activating factor is unknown. Bile acids which may be present in the serum, especially in cases of obstructive jaundice, decrease the activation of the phosphatase.

Thannhauser and his associates therefore pointed out that the mechanism producing an apparent increase in the serum phosphatase content in jaundice seemed to be understandable in the light of these findings. Any obstruction to the excretion of bile results in the damming up of both depressing (bile acids) and activating (cofactor) substances. Since the cofactor substances are more powerful as activators than are bile acids as depressors, the net result is an increase in activity of serum phosphatase. The difficulty of attempting to use phosphatase determinations in the differential diagnosis of hepatic disease is thus apparent.

### PORTAL HYPERTENSION

The two cardinal symptoms of hepatic disease are jaundice and ascites. The first usually is considered indicative either of biliary obstruction or of acute toxic or infectious hepatitis. The second is accepted as pathognomonic of hepatic cirrhosis.

The ascites in cirrhosis usually is accompanied by opsiuria (delayed excretion of urine), splenomegaly, hemorrhoids, gastrointestinal hemorrhages and the development of a collateral venous circulation over the abdomen. The clinical syndrome characterized by this set of signs and symptoms is observed in cases of hepatic cirrhosis but is not limited to such cases, for it may be seen in a miscellaneous group of other pathologic conditions. It is apparent that the common denominator responsible for the production of this clinical picture is that of engorgement of the portal circulation, with increased pressure in the portal vein. This syndrome, in consequence, has been called the syndrome of portal hypertension.

Though this syndrome is not discussed as such in many English and American textbooks, its recognition is not recent, for Stahl,[71] in 1698, described some of its cardinal features. There were many others who contributed to the study of the condition, but it remained for Gilbert,[72] in 1899, to crystallize clinical thought and to name the syndrome. The study of this condition has been furthered by the students

71. Stahl, G. E.: De vena portae, porta malorum hypochondriaco-splenetico-suffocativo-hysterico-colico-haemorrhoidariorum, Halle, 1698.

72. Gilbert, A., and Garnier, M.: De l'abaissement de la pression artérielle dans les cirrhoses alcooliques du foie, Presse méd. **1**:57, 1899.

of Gilbert and was discussed in detail in the monograph of Villaret and Justin-Besançon.[73]

The anatomy and physiology of the circulation of the liver and the changes which contribute to the development of vascular obstruction and portal hypertension in cases of portal cirrhosis have recently been summarized by McMichael,[74] McNee[75] and Weiss.[76] A consideration of the relations within the vascular bed of the liver was initiated by Gad,[77] in 1873. He maintained that the finer branches of the hepatic artery and of the portal vein met at an acute angle so that wedge-shaped flap valves were formed by this angle of union. This flap then shifted in accordance with the pressure on each side so that an increased flow of blood through the hepatic artery would limit the flow through the portal vein. McMichael[74] objected to this view as not being in keeping with the bulk of anatomic evidence. Herrick,[78] in 1907, perfused human livers, both normal and cirrhotic, with saline solution. He concluded that the increased portal pressure in hypertrophic portal cirrhosis is due not to vascular obstruction from fibrosis but to the combined effect of the direct communication of the arterial pressure to the portal vein through dilated capillaries and to the larger volume of flow through the hepatic artery proportional to the portal flow in the cirrhotic as compared with that in the normal liver. McIndoe,[79] on the other hand, reported that in cases of advanced hepatic cirrhosis the architecture of the liver is so disorganized that the parenchymal cells are almost completely divorced from the normal portal blood supply and are largely dependent on the hepatic artery for the maintenance of an adequate circulation. These changes he claimed were sufficient to explain the portal hypertension.

The studies of McIndoe were most convincing but did not tell the whole story. Bollman[80] has shown in dogs with damaged livers that

73. Villaret, M., and Justin-Besançon, L.: Le syndrome d'hypertension portale, in Roger, G. H.; Widal, F., and Teissier, P. J.: Nouveau traite de médecine, Paris, Masson & Cie, 1928, vol. 16, p. 97.

74. McMichael, J.: The Portal Circulation, J. Physiol. **75**:241, 1932.

75. McNee, J. W.: Liver and Spleen: Their Clinical and Pathological Associations, Brit. M. J. **1**:1017 (June 4); 1068 (June 11) 1932.

76. Weiss, S.: Portal Hypertension, Internat. Clin. **1**:149, 1932.

77. Gad, J.: Studien über Beziehungen des Blutstroms in der Pfortader zum Blutstrom in der Leberarterie, Inaug. dissert., Berlin, Gustave Schade, 1873.

78. Herrick, F. C.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93, 1907.

79. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. **5**:23 (Jan.) 1928.

80. Bollman, J. L.: The Influence of Diet on the Production of Ascites, Arch. Path. **6**:162 (July) 1928. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: VII. Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. **40**:471 (Oct.) 1927.

ascites may be produced or may be made to disappear at will by changes in the diet. Equally dramatic changes are seen in some patients as a result of the successful therapeutic use of mercurial diuretics. These changes are too rapid to be explained by the assumption that the ascites in portal cirrhosis is solely the result of portal obstruction from the fibrotic changes in the liver. Evidently other factors besides the degree of fibrosis affect the development of ascites. It is doubtful, however, if these accessory factors, which will be discussed later, can cause the development of ascites without the concomitant presence of portal obstruction.

Other conditions which may present the clinical syndrome of chronic portal obstruction with portal hypertension include thrombosis or phlebitis of the portal vein. Weir and Beaver [81] reviewed 127 cases, including 54 cases of simple thrombosis. In 7 cases in which there was cardiac disease the thrombosis was complete enough to cause death. Symptoms developed acutely, and in all cases there was infarction of the small intestine. Infarction of the liver, on the other hand, did not follow thrombosis of the portal vein but developed only after occlusion of the hepatic artery. In some cases Weir and Beaver noted the development of a collateral circulation around the portal obstruction. Because they found transitional stages they interpreted thickening of the wall of the portal vein as part of the thrombotic process rather than as a primary degeneration of the wall of the vein.

Klemperer [82] reviewed the literature on cavernomatous transformation of the portal vein and reported an additional case in which there were the symptoms of portal hypertension. He reported that these cases fell into three groups representing: (1) the end result of portal thrombosis, (2) malformations and (3) tumor (angioma) of the vein. Simonds [83] has also reviewed the effects of chronic occlusion of the portal vein, and Wilson and Lederer [84] have described the microscopic anatomy and pathogenesis of portal phlebosclerosis.

The most interesting group of cases in which there is the syndrome of portal hypertension is that ill defined group characterized by splenomegaly, anemia, leukopenia and frequently cirrhosis of the liver,

81. Weir, J. F., and Beaver, D. C.: Diseases of the Portal Vein: A Review of One Hundred and Twenty-Seven Instances, Am. J. Digest. Dis. & Nutrition **1**: 498, 1934.

82. Klemperer, P.: Cavernomatous Transformation of the Portal Vein: Its Relation to Banti's Disease, Arch. Path. **6**:353 (Sept.) 1928.

83. Simonds, J. P.: Chronic Occlusion of the Portal Vein, Arch. Surg. **33**:397 (Sept.) 1936.

84. Wilson, S. J., and Lederer, M.: Splenomegaly Portal Phlebosclerosis, Am. J. Dis. Child. **38**:1231 (Dec.) 1929.

as well as by changes in the portal circulation. The syndrome in this group of cases does not correspond accurately to the syndrome described by Banti, yet for want of a better term it is often discussed under the title of Banti's syndrome. According to some observers, cases of portal (Laënnec's, atrophic, alcoholic) cirrhosis properly belong in this group, apparent differences being due to variations in the order and time relations in the development of the disease. In many cases of so-called Banti's disease an etiologic factor, such as portal thrombosis, syphilis, adhesions or splenic ptosis, can be demonstrated, but in others the cause escapes detection.

There have been many theories to explain the origin of splenomegaly in the Banti syndrome. Toxic, inflammatory and compensatory factors have all been suggested as causal. More attention has been paid recently to the theory that the splenic changes, in part at least, are congestive and associated with portal hypertension. This theory has been stressed because of (1) the similarity of the clinical course in all cases in this group regardless of the primary cause, (2) the similarity of the pathologic changes, (3) the similarity of the response to splenectomy when performed in comparable stages of the disease and (4) the evidence for the existence of portal hypertension in all.

### CONGESTIVE SPLENOMEGALY

Many observers have emphasized the clinical similarity of the cases in this group. Eppinger stressed the congestive changes in the spleen. Larrabee [85] reviewed 47 cases which fell into this group and in all of which similar clinical features were present independent of the underlying etiologic process. He advocated early splenectomy in consequence. Engelbreth-Holm [86] presented several cases of tuberculous splenomegaly which clinically resembled cases of Banti's disease. In 2 of these the condition was relieved symptomatically after splenectomy. The pathologic changes in the spleen in cases of the Banti syndrome show a striking uniformity. This was stressed by Mallory,[87] who concluded that the histologic changes in the spleen could be accounted for by long-continued passive congestion. He pointed out the frequency with which an old thrombosis of the splenic vein may be overlooked and described a case in which an old recanalized throm-

85. Larrabee, R. C.: Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, Am. J. M. Sc. **188**:745, 1934.

86. Engelbreth-Holm, J.: A Study of Tuberculous Splenomegaly and Splenogenic Controlling of the Cell Emission from the Bone Marrow, Am. J. M. Sc. **195**:32, 1938.

87. Splenic Anemia, Cabot Case 20521, New England J. Med. **211**:1215, 1934.

bosis was recognized only by careful study of a series of microscopic sections. Eppinger likewise discussed the influence of venous stasis and the *Stauungsmilz* at length. Rousselot [88] reported that the characteristic microscopic changes in the spleen were scarring and the obliteration of the usual architecture. The cellular elements in both red and white pulp were decreased. The fibrosis included capsular and trabecular thickening together with interstitial fibrosis and so-called fibroadenia of Banti. There was a diminution in the number and in the size of the malpighian corpuscles.

Rousselot also emphasized the observation of dilatation and tortuosity of the veins in the splenic pedicle, the veins sometimes dilating to two to four times the normal diameter. Such changes were present in nearly all the cases reported by Rousselot, though in only half of them was there evidence of obstruction at the time of operation.

McMichael [89] postulated the identity of the siderotic nodule, the periarterial fibrosis and the Banti fibroadenia in the spleen. He concluded that the vascular changes in the spleen and the concomitant endophlebitis were due in part to an increase in the portal pressure. He also reported that microscopic or clinical evidences of hepatitis could be demonstrated in many cases in which there was no obvious cirrhosis. His experimental studies on cats [74] showed that the injection of epinephrine produced vasoconstriction of the intrahepatic branches of the portal vein, with a consequent rise in the portal pressure. Such observations are important, for some such mechanism acting in response to humoral or nervous stimulation may be responsible for increases in portal pressure in the absence of anatomically demonstrable obstruction.

The similarity of the pathologic changes in the spleen in cases of Banti's syndrome with those produced by experimentally induced venous congestion in animals as reported by McMichael [74] and Jäger [90] affords indirect evidence for the existence of portal congestion in these cases. Numerous investigators, including Carnot, Gayet and Merklen,[91] have measured the venous pressure in the portal vein in experimental animals.

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88. Rousselot, L. M.: The Rôle of Congestion (Portal Hypertension) in So-Called Banti's Syndrome, J. A. M. A. **107**:1788 (Nov. 28) 1936.

89. McMichael, J.: The Pathology of Hepato-Lineal Fibrosis, J. Path. & Bact. **39**:481, 1934.

90. Jäger, E.: Ueber Stauungsmilz, Verhandl. d. deutsch. path. Gesellsch. **26**:334, 1931.

91. Carnot, P.; Gayet, R., and Merklen, F. P.: Exploration graphique des modifications de la pression veineuse porte liées à des excitations vaso-constrictives, Compt. rend. Soc. de biol. **104**:1260, 1930.

Thompson and his associates [92] have extended these studies to man. They determined the pressure in the splenic vein at operation by direct venipuncture after the operative delivery of the spleen and before ligation of any of the larger vessels. In 3 cases of typical hemolytic jaundice the pressure in the splenic vein did not rise above 125 mm. of saline solution. In 8 cases in which there was the clinical syndrome of portal hypertension, the pressure in the splenic vein ranged from 250 to 500 mm. of saline solution. The venous pressure in the antecubital veins, taken at the same time, ranged from 12 to 140 mm. Five of the cases of portal hypertension were due to the Laënnec type of portal cirrhosis and 3 to cirrhosis from chronic schistosomiasis. It is to be hoped that studies such as these will be extended. They afford a direct measurement of the portal pressure in man which is obtainable in no other way. By demonstrating the presence of an increased pressure in the splenic vein in cases of the so-called syndrome of portal hypertension they have gone far in establishing the validity of a clinical picture which was established originally on a basis of logical deduction from indirect evidence.

The factor of venous stasis apparently does not explain the whole of the reaction of the spleen to venous congestion or the production of the associated clinical and hematologic pictures. Obstruction of short duration will not cause continued splenic enlargement, and Warthin [93] was unable to produce permanent splenomegaly by ligation of the splenic vein. The spleen may be enlarged in cases of cardiac failure but rarely to such degree that it is palpable below the costal margin. Possibly this is due to the relative short duration of the cardiac type of chronic passive congestion, for Larrabee considered five to six years the minimum time necessary for the production of the typical syndrome. Wohlwill [94] emphasized the fact that definite splenic thrombosis is not always accompanied by splenomegaly.

Jäger [95] remarked that recent work on the "reservoir function" of the spleen has shown great variation in different animal species as to the ratio between the capacity of the distended spleen and that of the contracted organ. It is therefore impossible to apply the experimental figures obtained for lower animals directly to man. An approximate

92. Thompson, W. P.; Caughey, J. L.; Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), J. Clin. Investigation **16**:571, 1937.

93. Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease, Internat. Clin. **4**:189, 1910.

94. Wohlwill, F.: Ueber Pfortadersklerose und Bantiähnliche Erkrankungen, Virchows Arch. f. path. Anat. **254**:243, 1925.

95. Jäger, E.: Milzbau und Kreislaufstörung, Virchows Arch. f. path. Anat. **299**:531, 1937.

estimate of the effect of acute venous congestion on the human spleen may be obtained by distending the normal organ with saline solution. The distended spleen may triple its original weight, and it is unlikely that chronic venous congestion produces a greater degree of enlargement. On this assumption an average normal adult spleen weighing 150 Gm. could enlarge to 450 Gm. in response to chronic congestion. The finding of additional proliferative changes in larger spleens than this led Jäger to suggest that while congestion alone would not produce marked splenomegaly (over 400 Gm.) in an adult, it might initiate a series of additional pathologic changes to account for further increase in the size of that organ. Johnston [96] added that the age of the patient often determines the degree of splenomegaly, for when an obstructive factor is present the splenomegaly is greater in the younger patients. It must also be remembered that the clinical degree of splenomegaly is variable. The spleen will cease to be palpable during or immediately after a gastric hemorrhage, only to enlarge again after its cessation or after a transfusion. This is a clinical observation of some importance.

### BLOOD FLOW IN THE PORTAL VEIN

The anatomic arrangement of the vascular supply within the liver has been studied in detail since the observations of Glisson [97] and other early anatomists. The profuse nature of the vascular supply has best been shown by the studies of Copher and Dick,[98] who found that the volume of the portal blood flow in dogs corresponds to 60 cc. of blood per minute per hundred grams of liver. Higgins, Mann and Priestley [99] said they considered this of fundamental importance, for they showed that while in normal animals hepatic tissue is regenerated rapidly after surgical excision, the presence of an Eck fistula prevents such regeneration. Furthermore, in fowls, in which there is free portocaval communication, excision of part of the liver does not lead to rapid regeneration of the remaining portion. They concluded, therefore, that the necessity of providing a capillary bed adequate to take care of the large portal blood flow is one of the essential factors in producing regeneration of the liver in normal experimental animals.

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96. Johnston, J. M.: Relation of Changes in the Portal Circulation to Splenomegaly of Banti's Type, Ann. Int. Med. **4**:772, 1931.

97. Glisson, F.: Anatomia hepatitis, The Hague, Arnold Leers, 1681, pp. 349-350, figs. 1 and 2.

98. Copher, G. H., and Dick, B. M.: "Streamline" Phenomena in the Portal Vein and the Selective Distribution of Portal Blood in the Liver, Arch. Surg. **17**:408 (Sept.) 1928.

99. Higgins, G. M.; Mann, F. C., and Priestley, J. T.: Experimental Pathology of the Liver: X. Restoration of the Liver of the Domestic Fowl, Arch. Path. **14**:491 (Oct.) 1932.

In man the blood flow through the portal vein has not been studied directly. Glenard,[100] in 1890, observed that certain diseases have predilections for one lobe of the liver or the other. Tumor metastases, for example, sometimes affect one lobe to the exclusion of the other. Glenard therefore postulated differences between the right and the left lobe of the liver.

Physiologic differences between the two lobes were demonstrated by Copher, Dick and Koechig,[101] who showed that the right lobe of the liver produced a greater volume of bile per gram of hepatic tissue than did the left lobe but that the latter produced a more concentrated bile.

A partial anatomic explanation was afforded by McIndoe and Counseller,[102] who studied the vascular supply of the liver by means of corrosion methods. They found that the right and the left branches of the portal vein supply separate portions of hepatic tissue, with no intercommunication. The two portions are sharply divided by the embryologic boundary between the right and the left lobe, which lies along a line from the fossa of the gallbladder to the entrance of the hepatic veins into the vena cava.

That there might be a similar separation in the distribution of blood flowing into the portal vein from the different branches was first demonstrated by Sérégé,[103] in 1901. He injected india ink into the splenic vein of a dog and found that it was deposited only in the left lobe of the liver. Bartlett, Corper and Long[104] injected emulsified olive oil into the splenic vein and likewise found that it was deposited in that area. They suggested that this specific distribution might be due to "streamlining" of the blood from the different tributaries of the portal vein.

Copher and Dick studied this phenomenon by the injection of a solution of trypan blue, which provides immediate visualization of the stained area. They were able to demonstrate at least three separate currents in the portal vein, coming from the splenic and from the large and the small mesenteric veins, respectively. Blood from the spleen, stomach and colon was distributed to the left lobe of the liver. Blood

100. Glenard, F.: Des resultats de l'exploration du foie chez les diabètiques, Lyon méd. **44**:5, 1890.

101. Copher, G. H.; Dick, B., and Koechig, I.: Differences in Bile from the Two Sides of the Liver, Am. J. Physiol. **87**:510, 1928.

102. McIndoe, A. H., and Counseller, V. S.: Bilaterality of the Liver, Arch. Surg. **15**:589 (Oct.) 1927.

103. Sérégé, H.: Contribution à l'étude de la circulation du sang porte dans le foie et des localizations lobaires hépatiques, J. de méd. de Bordeaux **31**:271, 1901.

104. Bartlett, F. K.; Corper, H. J., and Long, E. R.: The Independence of the Lobes of the Liver, Am. J. Physiol. **35**:36, 1914.

from veins draining the duodenum, pancreas and jejunum, thus including those sections of the intestinal canal primarily concerned in the digestion and absorption of foodstuffs, drained only into the right lobe of the liver.

The question of "streamlining" in the venous system has been studied even more extensively by Franklin and McLachlin,[105] who have demonstrated this phenomenon in other veins beside the portal.

The technic of roentgen cinematographic methods applicable to the study of the circulation was developed by Naegeli and Janker,[106] and the methods have been described by Janker.[107] Franklin and Janker[108] applied these methods to the study of blood flow in the portal and hepatic veins of animals. They found that during inspiration the blood flow from the liver into the hepatic veins is increased and that there is simultaneous blockage of the return along the vena cava, for the shadow cast by the intrahepatic portion of the inferior vena cava was narrowed during inspiration. This apparent narrowing indicated either actual compression of the vessel or else displacement of the caval flow by the influx of a streamlined flow from the hepatic veins.

### COLLATERAL CIRCULATION

Acute and complete occlusion of the portal vein is incompatible with life, whether observed in patients as a result of thrombosis or produced experimentally in animals, as reported by Boyce, Lampert and McFetridge.[109] Partial occlusion is not. If the occlusion is produced so gradually as to permit the development of venous collaterals, it may become complete without a fatal termination.

The course and the extent of the collateral circulation which develops in consequence of portal obstruction or hypertension are well known. The cutaneous vessels over the abdomen and back become distended and in extreme cases may go on to the formation of true caput medusae.

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105. Franklin, K. J., and McLachlin, A. D.: Streamlines in the Abdominal Vena Cava, J. Physiol. **86**:386, 1936.

106. Naegeli, T., and Janker, R.: Experimentell-röntgenologische und röntgenkinematographische Kreislaufstudien, Deutsche Ztschr. f. Chir. **232**:560, 1931.

107. Janker, R.: Die Röntgenkinematographie, ein Forschungs- und Lehrmittel, Deutsche Ztschr. f. Chir. **240**:52, 1933.

108. Franklin, K. J., and Janker, R.: Effects of Respiration upon the Venae Cavae of Certain Mammals, as Studied by Means of X-Ray Cinematography, J. Physiol. **81**:434, 1934; Respiration and the Venae Cavae, ibid. **86**:264, 1936; The Effect of Respiration upon the Circulation Through the Liver, as Studied by Means of X-Ray Cinematography, ibid. **89**:160, 1937.

109. Boyce, F. F.; Lampert, R., and McFetridge, E. M.: Occlusion of the Portal Vein: Experimental Study with Its Clinical Application, J. Lab. & Clin. Med. **20**:935, 1935.

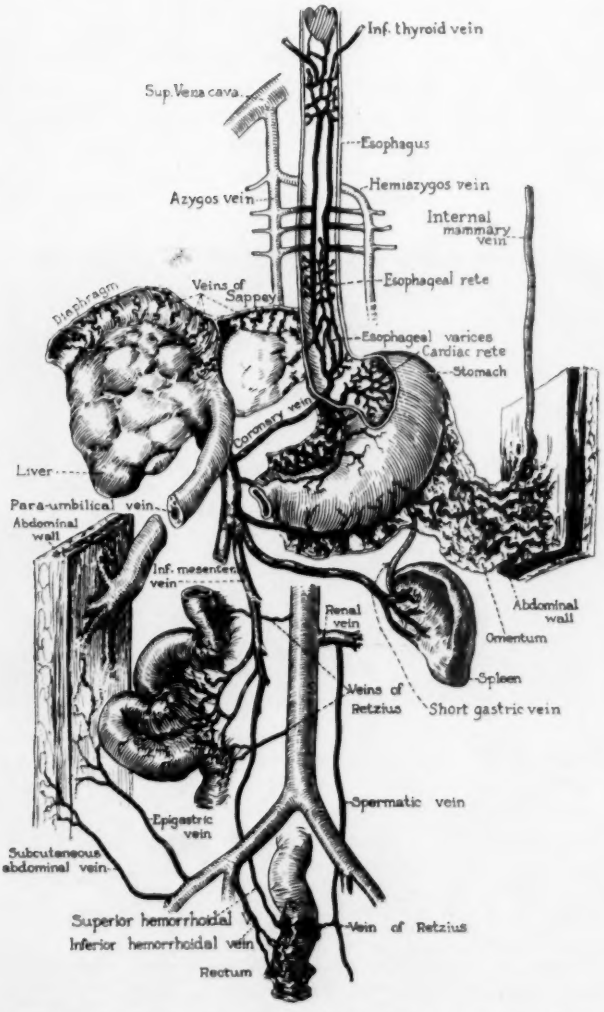


Fig. 5.—Diagram of the collateral venous circulation in portal cirrhosis, with especial reference to the anatomic features of the esophageal varices.

The presence of venous distention in the latter condition is obvious, but the initial stages of the development of a collateral circulation often require careful examination for their recognition. In such cases the use of infra-red photography is a valuable clinical adjunct. This was introduced by Rawling,[110] who pointed out that the maximal spectral transmission of light rays by the skin takes place in the infra-red zone. When venous congestion is present the veins are distended, and the contained blood is more venous in character. When photographed by the infra-red method, the veins therefore stand out more vividly than normal. Barker and Julin,[111] Payne,[112] Jones [113] and others [114] have

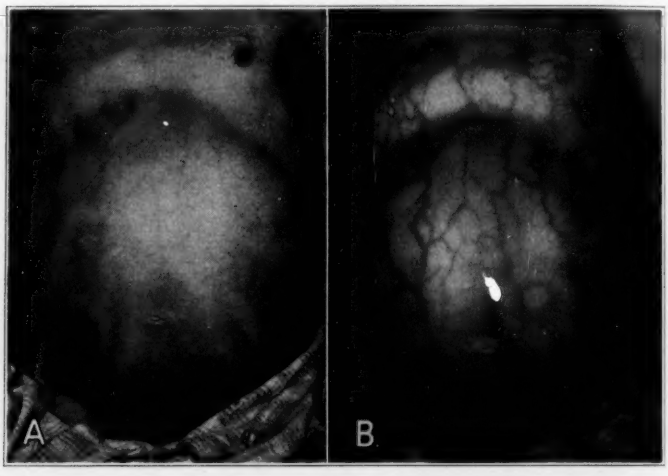


Fig. 6.—The collateral venous circulation over the abdomen in a case of portal cirrhosis with ascites. *A*, photographed by the ordinary method; *B*, photographed by the infra-red method (authors' case).

used this method for studying superficial venous distention, such as accompanies portal hypertension.

110. Rawling, S. O.: Infra-Red Photography, London, Blackie & Son, Ltd., 1933.

111. Barker, N. W., and Julin, L. A.: Demonstration of Superficial Veins by Infra-Red Photography, Proc. Staff Meet., Mayo Clin. **9**:58, 1934.

112. Payne, R. T.: Infra-Red Photography of the Superficial Venous System, Lancet **1**:235, 1934.

113. Jones, E.: Demonstration of Collateral Venous Circulation in the Abdominal Wall by Means of Infra-Red Photography, Am. J. M. Sc. **190**:478, 1935.

114. Weisswange, W. M. H., and Friedrich, A.: Versuche mit Infrarotaufnahmen in der Medizin, Deutsche med. Wchnschr. **62**:1540, 1936.

### VENOUS BRUIT

When the collateral circulation is well developed a soft continuous bruit or hum may occasionally be heard over the abdomen; usually it is heard in the neighborhood of the xiphoid or of the umbilicus. First reported by Pégot,[115] Bamberger [116] and Trousseau,[117] it was later discussed in detail by Thayer.[118] Bates [119] recently reported a case in which the bruit was heard at about the level at which the vena cava pierces the diaphragm. He, like Piazza-Martini,[120] concluded that this bruit was due to constriction of the inferior vena cava in its passage through the liver. Kenawy [121] reported 6 additional cases of bilharzial cirrhosis in which a venous hum was present. In all the murmur was a localized continuous venous hum, frequently accompanied with a thrill. It was louder when the patient was sitting or standing than when he was recumbent. It was not associated with any primary cardiovascular abnormality. There was no relation between the intensity of the bruit and the presence of ascites or anemia. In one case the murmur disappeared after splenectomy. Kenawy concluded that this probably was due to the severance of some venous communication at the time of operation. In the majority of cases it seems as if the nature and the position of the hum were determined by the location and the character of the venous collaterals rather than by caval obstruction.

### ESOPHAGEAL VARICES

The development of esophageal varices in cases of hepatic cirrhosis or of portal hypertension is well known, as is the danger of serious or fatal hematemesis from the rupture of such a varix. Plotz and Reich [122] have considered this subject in some detail and have emphasized the importance of the early demonstration of such varices in the diagnosis of portal hypertension.

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115. Pégot: Tumor variqueuse, avec anomalie du systeme veineux et persistence de la veine ombilicale, development des veines sous-cutanées abdominales, Bull. Soc. anat. de Paris **18**:49, 1833.

116. Bamberger, H.: Granulierte Leber, Wien. med. Wchnschr. **1**:5, 1851.

117. Trousseau, A.: Lectures on Clinical Medicine, ed. 3, translated by J. R. Cormack, London, New Sydenham Society, 1872, vol. 5, p. 131.

118. Thayer, W. S.: On the Presence of a Venous Hum in the Epigastrium in Cirrhosis of the Liver, Am. J. M. Sc. **141**:313, 1911.

119. Bates, J. L.: Continuous Venous Hum in Cirrhosis of the Liver, Lancet **1**:1108, 1937.

120. Piazza-Martini, V.: Del rumore di soffio venoso udibile sull area epatica, Riforma med. **10**:663, 1894.

121. Kenawy, M. R.: Continuous Venous Hum in Bilharzial Cirrhosis of the Liver, Lancet **1**:1281, 1937.

122. Plotz, M., and Reich, N.: Esophageal Varices in Portal Hypertension, Am. J. Digest. Dis. & Nutrition, to be published.

The anatomy and pathogenesis of esophageal varices have been studied carefully by Kegaries.[123] The anastomosis on the portal side is composed of vessels from the coronary vein or veins and from the left gastroepiploic veins and the vasa brevia, which form a cardiac rete in the upper third of the stomach. This second group of vessels is especially involved in some cases of splenic disease and may explain

Fig. 7.—Roentgenographic demonstration of the esophageal varices in a case of portal cirrhosis (authors' case).

the hemorrhage that occasionally follows ligation of the coronary vein or splenectomy. At the cardia the veins are supported by a thick muscularis mucosae, and the mucosa is closely adherent to the sub-

123. Kegaries, D. L.: Venous Plexus of the Esophagus, Surg., Gynec. & Obst. **58**:46, 1934.

mucosa. In the lowest third of the esophagus the rich venous anastomosis of the submucosa is poorly supported by connective tissue and hence is a most favorable site for the formation of varicosities.

The presence of esophageal varices may be inferred from hematemesis or may be demonstrated either by esophagoscopic [124] or roentgenographic methods.

Fig. 8.—Roentgenographic demonstration of the esophageal varices in a case of portal cirrhosis (authors' case).

The latter method is increasing in favor and has been reported on by Schatzki,[125] Oppenheimer [126] and Brdiczka and Tschakert.[127] Three

124. Moyer, S. J.: Esophagoscopic Study of Esophageal Varices, Arch. Otolaryng. **10**:409 (Oct.) 1929.

125. Schatzki, R.: Relief Studies of the Normal and Abnormal Esophagus, Stockholm, P. A. Norstedt & Söner, 1936.

126. Oppenheimer, A.: Esophageal Varices, Am. J. Roentgenol. **38**:403, 1937.

127. Brdiczka, I. G., and Tschakert, J.: The X-Ray Diagnosis of Esophageal Varices, Fortschr. a. d. Geb. d. Röntgenstrahlen **46**:156, 1932.

stages have been recognized in the roentgenologic studies, although these sometimes merge into each other or may be seen on the same plate: (1) the early stage, marked by a slight and diffuse venous congestion, resulting in moderate broadening of the rugae of the lower part of the esophagus; (2) beginning dilatation of larger individual veins which emerge from the submucosa and are marked by small rounded defects seen in the relief of the lowest portion of the esophagus, and (3) generalized enlargement of numerous veins which encroach on the mucosa. In the latter period the typical vermiform "negative shadows," or spaces, predominate. Successful visualization depends on several factors. The films should be exposed during forced inspiration, as the varices are distended at that time. They are seen most easily during the short interval between swallowing and complete emptying of the esophagus. The delay in the passage of the barium sulfate meal through the esophagus ranges from a second or two in early stages of congestion to several hours in the later stages, with superimposed cardiospasm. The esophageal stasis may be produced either by the mechanical obstruction of the varices or by the cardiospasm. The presence of food particles, polyps, a malignant growth, syphilis or cardiospasm must be excluded in making a differential diagnosis. All these can usually be excluded on roentgenographic evidence alone. The development of the roentgen diagnosis of esophageal varices is one of the most significant recent advances in the diagnosis of conditions associated with portal hypertension.

### SURGICAL TREATMENT OF ASCITES AND HEMATEMESIS

There have been a multitude of attempts by surgeons to relieve the ascites and prevent hematemesis in cases of hepatic cirrhosis and portal hypertension. These have been reviewed by Zechel [128] in some detail. The main lines of surgical attack which have been suggested, either singly or in combination, are:

1. To promote drainage of the ascitic fluid out of the abdominal cavity into the bladder, pleural cavity, lumbar musculature, subcutaneous tissues or lymphatic or venous system by a variety of mechanical devices.

2. To establish a venous shunt around the liver by direct anastomosis between the portal vein and the inferior vena cava (Eck fistula) or their branches.

3. To further the development of a collateral circulation by visceropexy or omentopexy. This is one of the simplest operations from the standpoint of the surgical technic involved and thus far has been one of the most popular. In many cases the results are disappointing,

128. Zechel, G.: Cirrhosis of the Liver as a Surgical Problem, Illinois M. J. **70**:560, 1936.

but brilliant exceptions occur. Grinnell [129] reported that he had performed omentopexy in 23 cases of portal cirrhosis, with satisfactory results in 10.

4. To decrease the portal blood supply by vascular ligation. Splenectomy is the most popular operation of this type and is replacing ligation of the splenic vessels, though Watson [130] has recommended the latter. The types of cases reported are so varied and the experience of any individual surgeon is so slight that it is difficult to evaluate this operation from a study of the literature. Pemberton [131] reported that its value was established in the Banti syndrome, or splenic anemia. The results of splenectomy are less satisfactory when splenomegaly is complicated by well defined hepatic cirrhosis. Occasionally recovery is obtained in apparently hopeless cases, as in the one reported by Deaver and Reimann.[132] Mandel and Marcus [133] said they were encouraged by the results of splenectomy as a means of preventing gastrointestinal hemorrhages in cases of portal cirrhosis. Mayo,[134] on the other hand, found that, in general, the results after splenectomy were no better than those after omentopexy. Walters, Rowntree and McIndoe [135] tried to reduce the local blood flow and pressure in the esophageal plexus and so prevent the rupture of esophageal varices and resultant hematemesis by ligation of the coronary vein of the stomach. In a few cases the results were satisfactory, but the reported series was small. Venous connections between the spleen and the greater curvature of the stomach or large veins extending from the spleen along the under surface of the diaphragm may serve to provide an oversupply of blood to esophageal varices and produce recurrent hemorrhage after ligation of the coronary vein. It seems probable that if this operation is to be successful it must be combined with splenectomy, at least in certain cases.

5. To diminish transudation from the portal system into the peritoneal cavity and obliterate part of the portal bed by resection of a portion

129. Grinnell, R. S.: Omentopexy in Portal Cirrhosis of the Liver with Ascites: A Review of Twenty-Three Cases, Ann. Surg. **101**:891, 1935.

130. Watson, R. B.: Ligation of Splenic Artery for Advanced Splenic Anemia, Brit. M. J. **1**:821, 1935.

131. Pemberton, J. deJ.: Results of Splenectomy in Splenic Anaemia, Haemolytic Jaundice, and Haemorrhagic Purpura, Ann. Surg. **94**:755, 1931.

132. Deaver, J. B., and Reimann, S. P.: Splenic Enlargement with Cirrhosis of the Liver, Ann. Surg. **88**:355, 1928.

133. Mandel, E., and Marcus, G.: Zur Behandlung von Varicenblutungen bei Lebercirrhose durch Splenektomie, Ztschr. f. klin. Med. **128**:504, 1935.

134. Mayo, W. J.: Review of Five Hundred Splenectomies, Ann. Surg. **88**:409, 1928.

135. Walters, W.; Rowntree, L. G., and McIndoe, A. H.: Ligation of Coronary Veins for Bleeding Esophageal Varices, Proc. Staff Meet., Mayo Clin. **4**:146, 1929.

of the intestine. Fuller and her associates [136] reported a case in which the operation was successfully performed and the patient was free from ascites twenty-nine months after the resection of slightly less than 7 feet (213 cm.) of small intestine. This is a most radical procedure, and the reader is referred to their article for the arguments whereby they seek to justify its use.

One of the reasons why splenectomy has not been more popular in the treatment of portal hypertension and ascites has been the danger of postoperative thrombosis. Rosenthal [137] found great differences in the numbers of blood platelets and concluded that splenomegaly in part may represent an attempt to regulate the distribution of platelets. He further divided his cases with regard to thrombopenia and thrombocythemia. The prognosis was better in association with the former, and postoperative thrombosis was frequent in association with the latter. Evans [138] reported confirmatory results, while Graham Bryce [139] and Rousselot [88] did not find a correlation between the initial platelet count and the postoperative course. Moore,[140] Englebreth-Holm, and Smith and Farber [141] likewise reported cases which seemed to refute Rosenthal's hypothesis. Further study along this line, with a search for better preoperative prognostic criteria, is urgently indicated.

Another possible solution of the problem of postoperative thrombosis has been suggested by the work of Best and his colleagues,[142] who have prepared heparin with a purity suitable for intravenous use in quantity. The use of such a preparation to render the blood incoagulable or slowly coagulable, as suggested by Hedenius and Wilander,[143] promises to be of value in preventing thrombosis not only after splenectomy but after a wide range of surgical procedures.

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136. Fuller, M. K.; Cook, D. D. M.; Walter, O. M., and Zbitnoff, N.: Enterectomy in the Surgical Treatment of Hepatic Cirrhosis or Portal Obstruction with Ascites, Surg., Gynec. & Obst. **65**:331, 1937.

137. Rosenthal, N.: Clinical and Hematologic Studies on Banti's Disease: Blood Platelet Factor with Reference to Splenectomy, J. A. M. A. **84**:1887 (June 20) 1925.

138. Evans, W. H.: The Blood Platelets in Splenic Anemia, Lancet **1**:277, 1929.

139. Graham Bryce, A.: Splenectomy and Thrombosis, Lancet **2**:1423, 1932.

140. Moore, S. W.: Portal Thrombosis Following Splenectomy for Splenic Anemia, Surg., Gynec. & Obst. **63**:382, 1936.

141. Smith, R. M., and Farber, S.: Splenomegaly in Children with Early Hematemesis, J. Pediat. **7**:585, 1935.

142 Murray, W. G.; Jaques, L. B.; Perrett, T. S., and Best, C. H.: Heparin and Thrombosis of Veins Following Injury, Surgery **2**:163, 1937.

143. Hedenius, P., and Wilander, O.: The Influence of Intravenous Injections of Heparin in Man on the Time of Coagulation, Acta med. Scandinav. **88**:443, 1936.

ACCESSORY FACTORS IN THE PRODUCTION OF ASCITES

While the presence of mechanical obstruction to the passage of portal blood through the cirrhotic liver, with resultant portal hypertension, is universally accepted as a factor, it is doubtful if it alone is sufficient to account for the production of ascites. We have previously stressed the importance of accessory factors in the production of ascites, but the assignment of the role played by each is difficult. Chronic obstruction of the portal vein will not produce permanent ascites. It is likely that sufficient additional obstruction to produce temporary ascites results when the partial obstruction of cirrhosis is augmented by passive congestion, vasomotor disturbances, cloudy swelling of the hepatic parenchyma, serous hepatitis or thrombosis of the portal radicles in the liver. Chronic perihepatitis or peritonitis is a frequent concomitant of cirrhosis and may be responsible for some of the ascites. Toxic factors have been described as responsible for the development of ascites. These as yet undefined toxins may act either by increasing the degree of portal obstruction or by changing the capillary permeability of the portal area, thus allowing the transudation of a greater amount of fluid or interfering with its resorption.

The effect of changes in the serum protein is better understood. This subject was reviewed a year ago by Greene, Handelsman and Babey. They referred to the accumulated literature indicating that in hepatic disease and especially in cirrhosis there is a reduction in the serum protein content. The frequency with which the Takata-Ara [144] and similar tests give positive results indicates that there is a concomitant change in the serum proteins. This is also shown by the change in the viscosity of the blood serum reported by Kaunitz and Kent.[145] Furthermore, the experiments of Butt and Keys [146] and of Snell [147] showed that not only is the serum protein value decreased in cases of cirrhosis but there is a disproportionate reduction in the colloidal osmotic pressure. This change is in a direction which directly favors the production of ascites. Further evidence of the change in

144. Ucko, H.: Serum Test for Diagnosis of Liver Disturbances, Guy's Hosp. Rep. **86**:166, 1936. Magath, T. C.: The Takata-Ara Test of Liver Function, Am. J. Digest. Dis. & Nutrition **2**:713, 1936. Boccia, D., and Gamalero, J. A.: Takata-Ara Reaction in Internal Diseases, Semana méd. **2**:365, 1936.

145. Kaunitz, H., and Kent, H.: Relative Viscosity of Blood Serum in Persons With and Without Hepatic Disorders and Its Relation to Protein Content and Its Fractions, Ztschr. f. klin. Med. **132**:670, 1937.

146. Butt, H. R., and Keys, A.: Colloid Osmotic Pressure: Studies of Normal Individuals and of Those with Hypoproteinemia, Proc. Staff Meet., Mayo Clin. **12**:566, 1937.

147. Snell, A. M.: The Value to Clinical Medicine of Experimental Studies on the Liver, Ann. Int. Med. **11**:581, 1937.

the protein value has been furnished by Kendall.[148] He has analyzed human serum by means of specific antiserums and has found that the globulin fraction can be separated into at least two fractions which have distinct antigenic properties. Normal serum contains between 1.1 and 2.1 per cent of alpha globulin and between 0.4 and 1 per cent of globulin x. In patients with cirrhosis both the quantities and the proportions of these two are markedly changed from the normal. It is to be hoped that further work along these lines may clarify the role of changes in the serum protein values in the develoment of ascites.

148. Kendall, F. E.: Studies on Serum Proteins: I. Identification of a Single Serum Globulin by Immunological Means, Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, J. Clin. Investigation **16**:921, 1937.